2008
NASA OCCUPATIONAL HEALTH CONFERENCE

I. INFLAMMATION

And

ATHERSCLEROSIS

(ATHEROTHROMBOSIS)

II. NON INVASIVE EVALUATION OF CORONARY ARTERY DISEASE

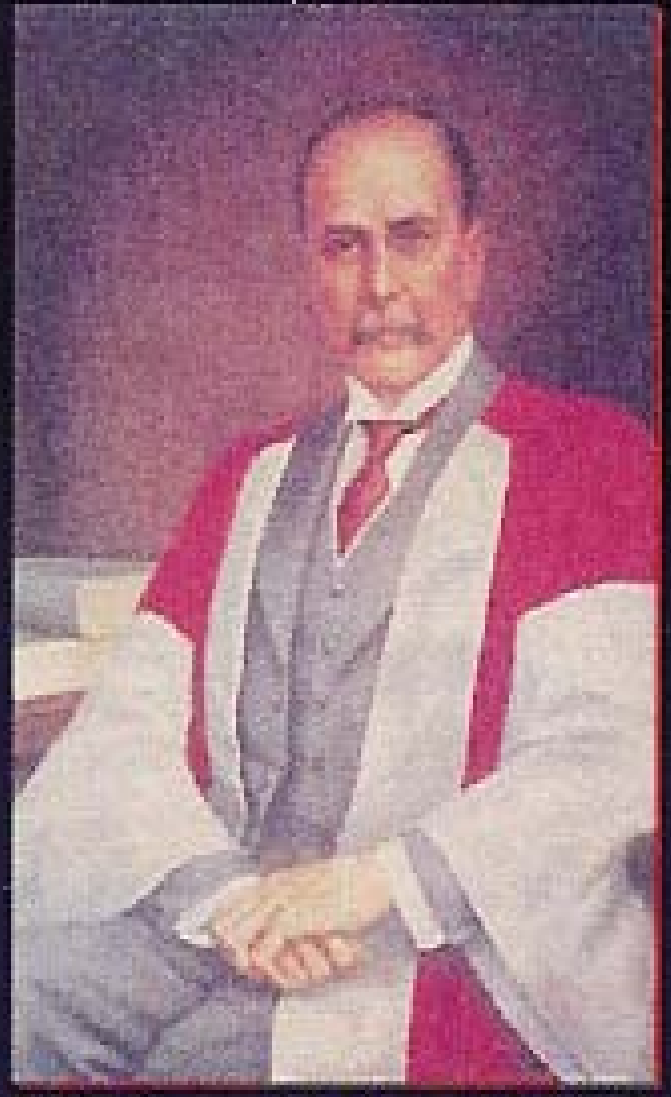
STEPHEN J. PLANTHOLT, MD, FACP, FACC
Midatlantic Cardiovascular Associates

Director of Cardiology
and
Cardiac Catheterization Laboratory

St. Agnes Hospital
Baltimore, Maryland

(stephenplantholt@comcast.net)


FEBRUARY 23, 2004
TIME
BUSH'S MILITARY RECORDS
IS DISNEY MOUSETRAPPED?
THE SECRET KILLER
■ The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER'S and other diseases
■ What you can do to fight it
www.time.com AOL Keyword: TIME



William Osler (1892)
The Principles and Practice of Medicine

"...in the make up of the machine, bad material was used for the tubing."

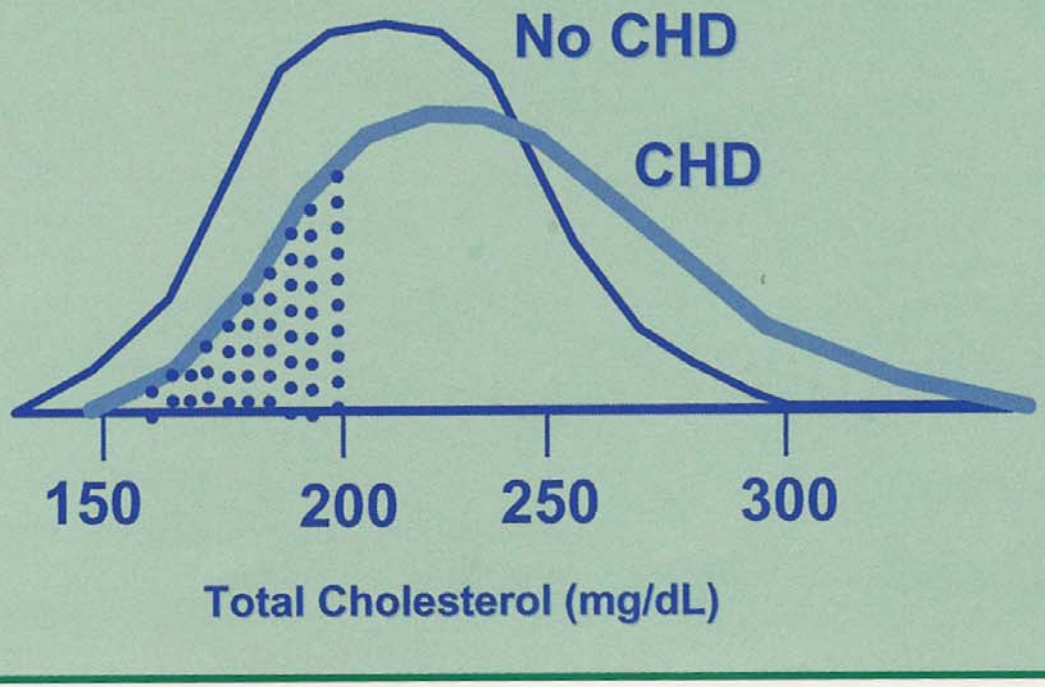
“ like rust in a pipe”

The Oslerian view of atherosclerosis:

FIGURE 1

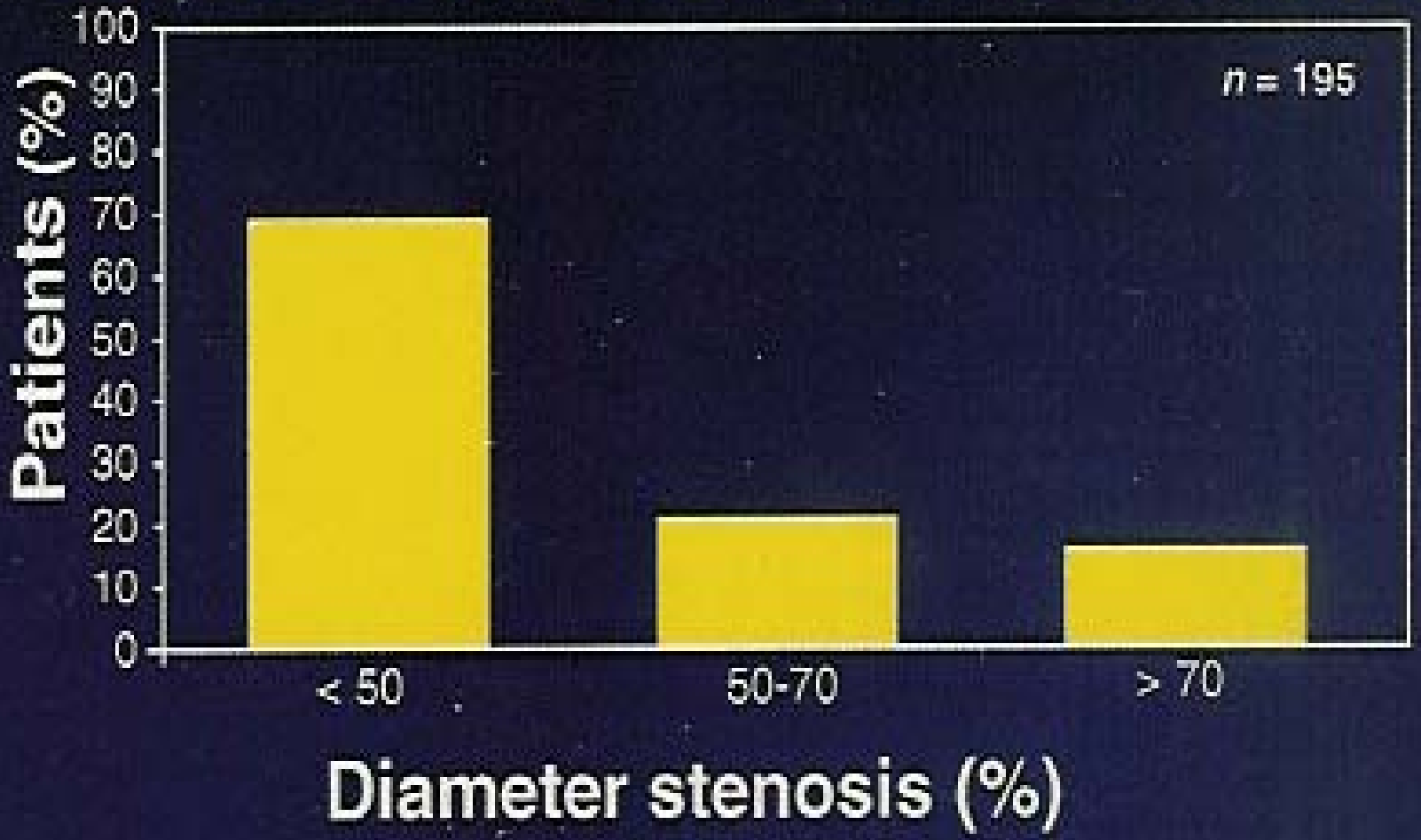
35% of CHD Occurs in People With Total Cholesterol < 200 mg/dL

Framingham Heart Study: 26-Year Follow-up

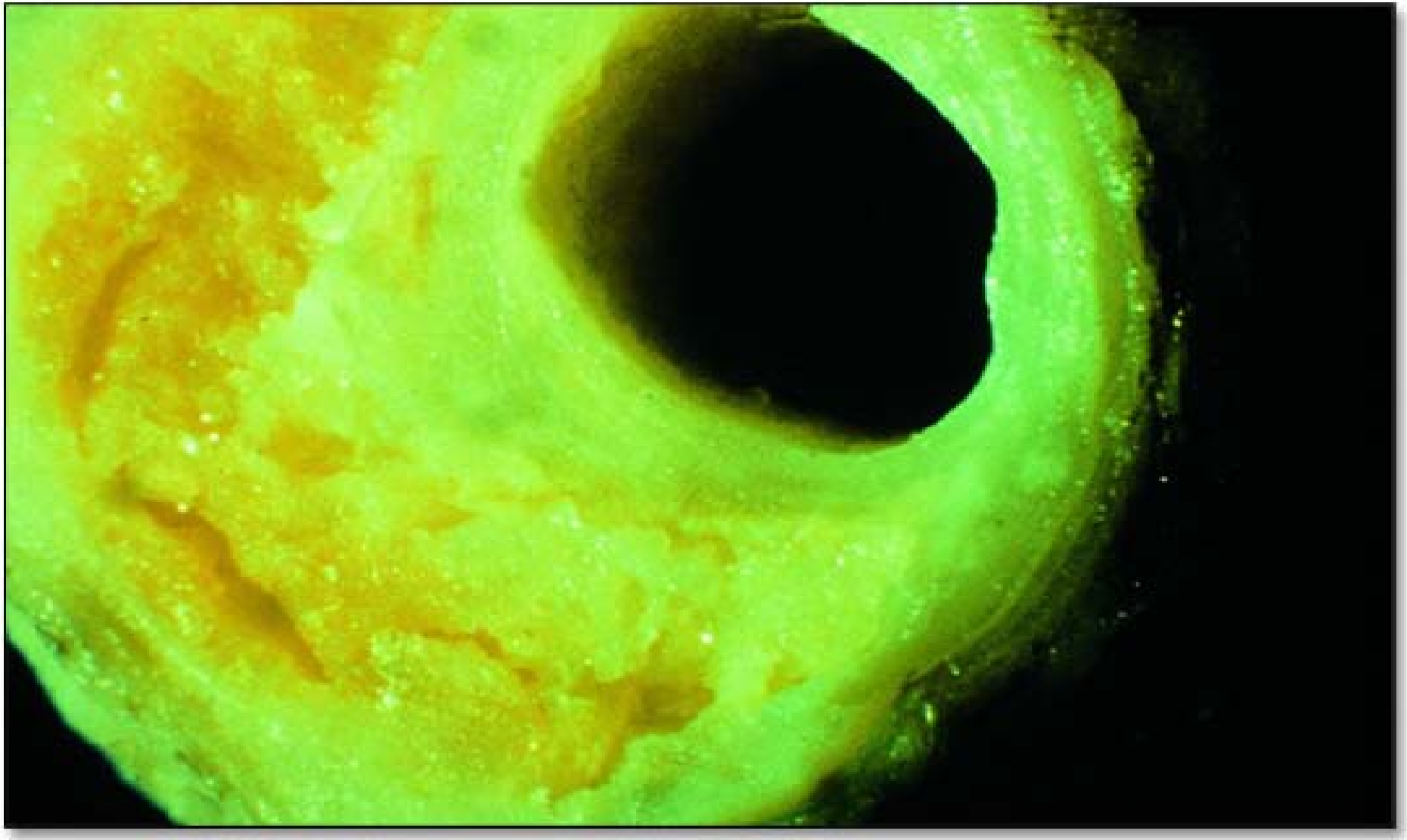


Adapted from: Castelli WP. Lipids, risk factors and ischaemic heart disease. *Atherosclerosis.* 1996;124:S1-S9.

Severity of coronary artery stenosis before acute MI



Data from four studies. *Smith SC. Circulation 1996*



Summary of Plaque Constituents

Lipid

Extracellular

Intracellular
(foam cells)

Macrophages

Connective Tissue Matrix

Collagen

Elastin

Proteoglycans

Cells

Smooth Muscle

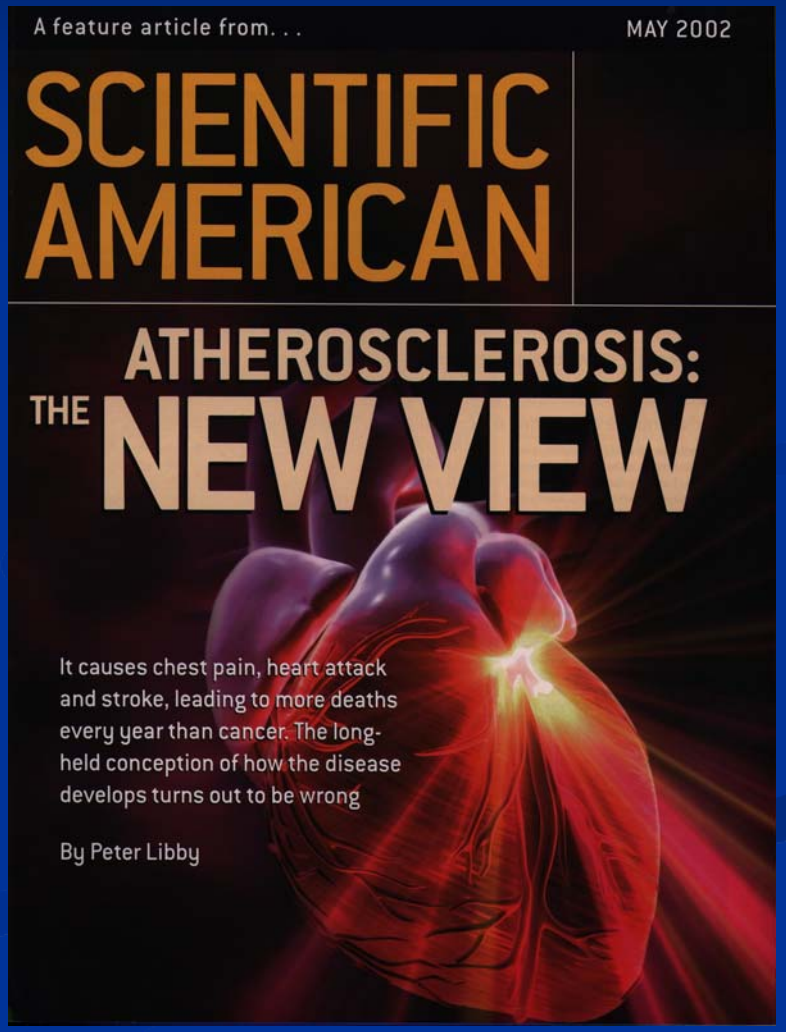
T Lymphocyte

Mast (basophil)

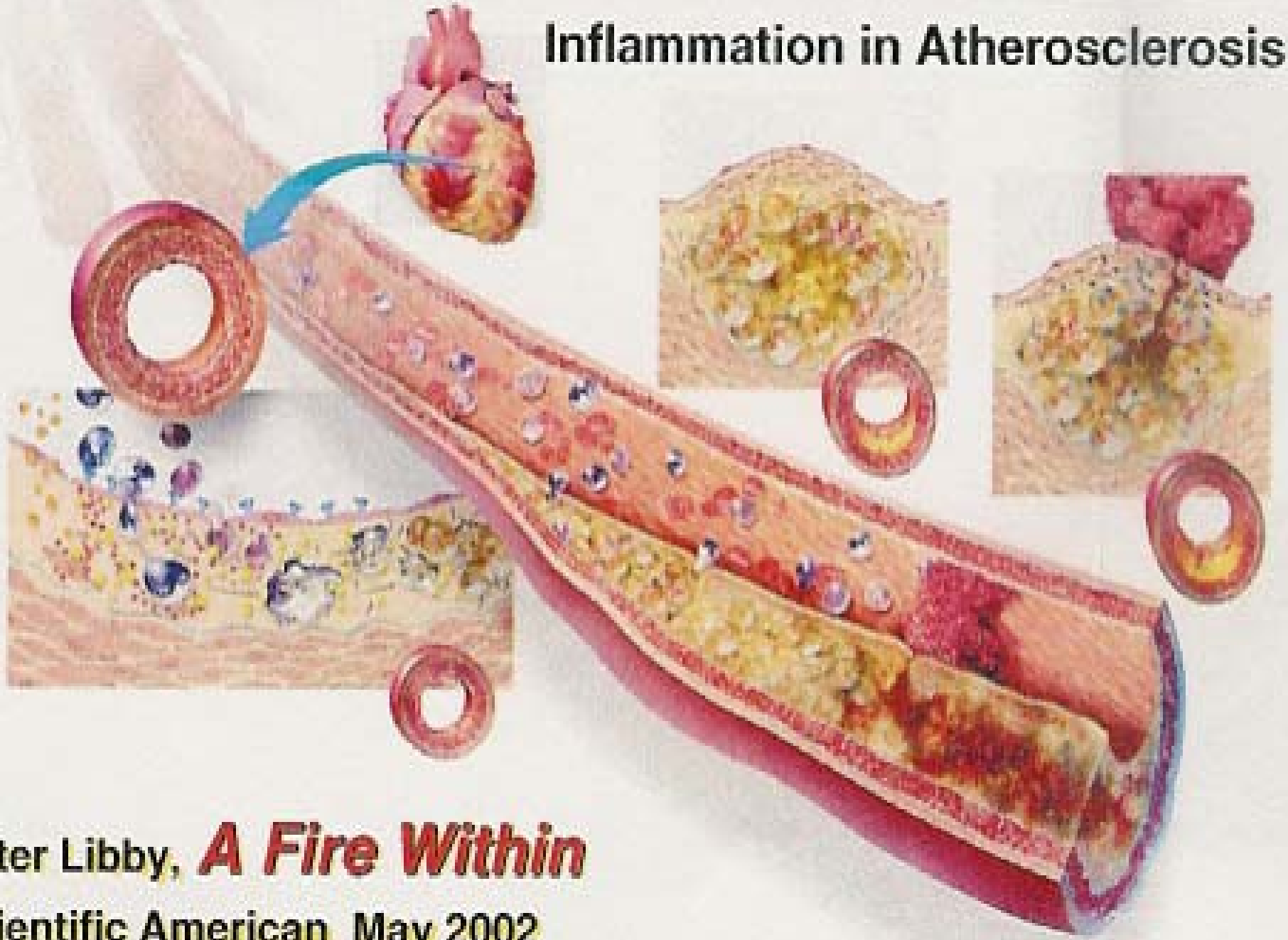
Atherosclerosis: An Inflammatory Disease

- The story extends beyond dyslipidemia
- "…inflammation fuels the development and progression of atherosclerosis…"
- A common pathway for atherosclerosis risk factors

– Peter Libby, Scientific American, May 2002



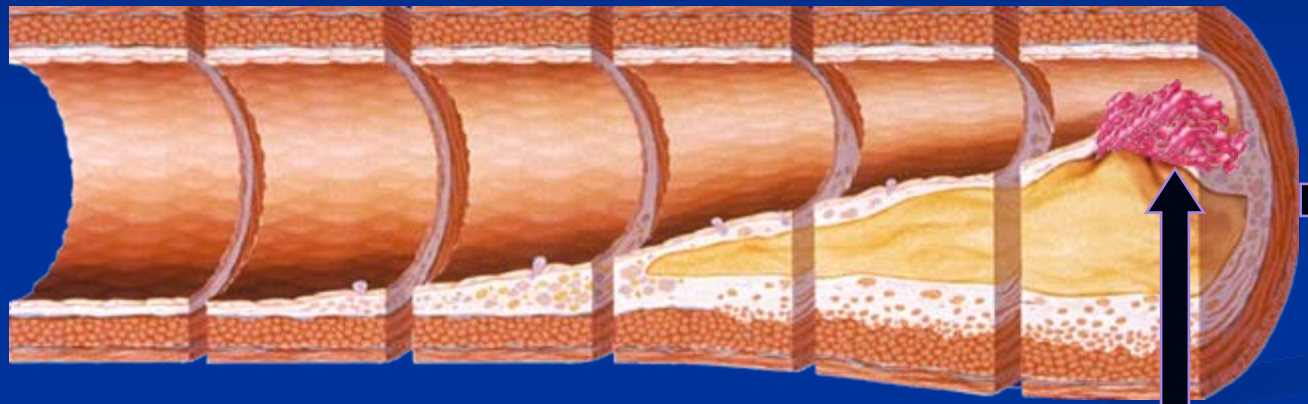
Inflammation in Atherosclerosis



Peter Libby, ***A Fire Within***

Scientific American May 2002

Vascular Disease: A Generalized and Progressive Process



Atherosclerosis

Thrombosis

- Unstable angina
- MI

(ACS)

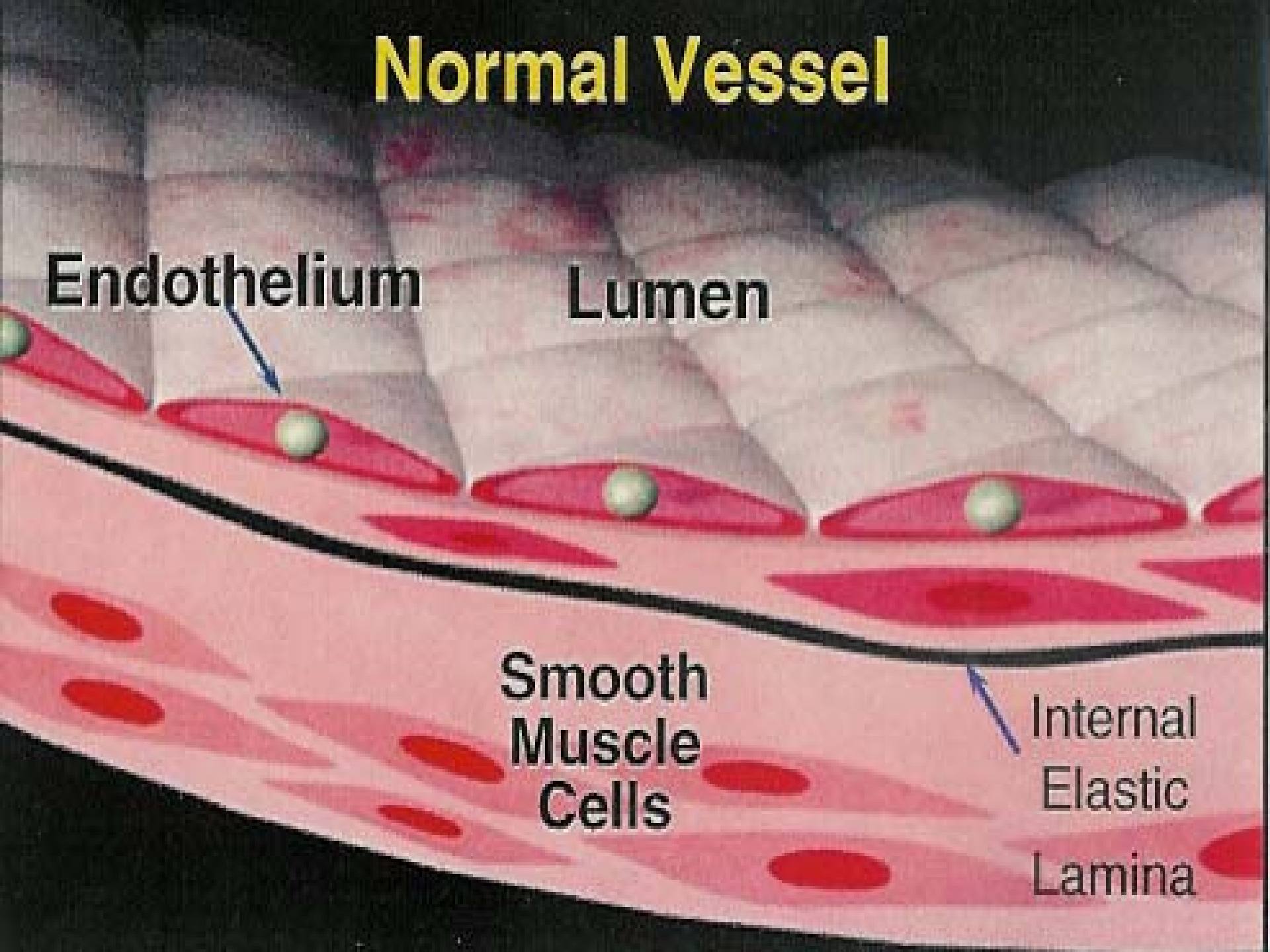
- Ischemic stroke/TIA
- Critical leg ischemia
- Cardiovascular death

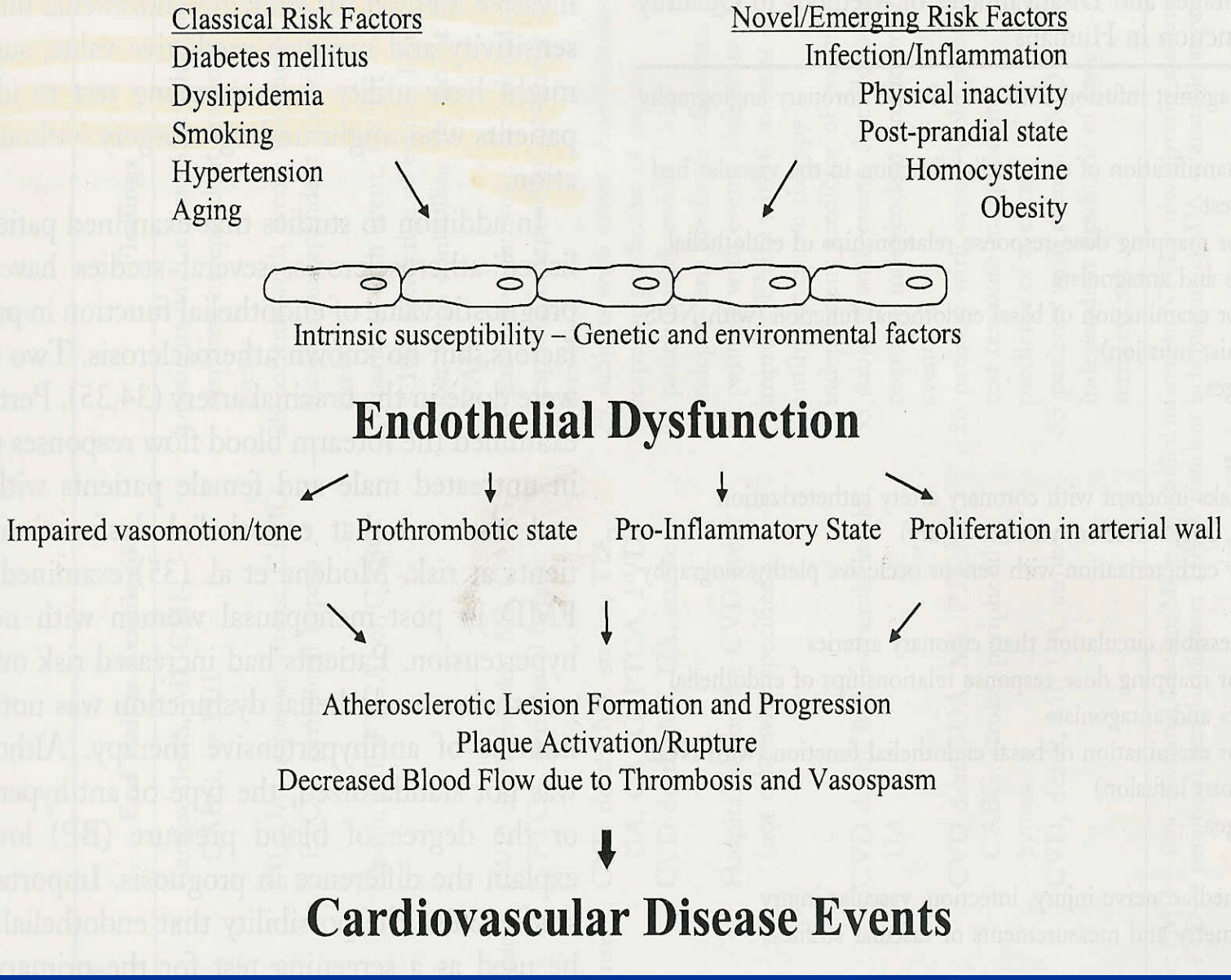
Stable angina
Intermittent claudication

Adapted from Stary HC et al. *Circulation*. 1995;92:1355-1374 and Fuster V. *Vasc Med*. 1998;3:231-239.

Inflammation and Atherosclerosis

I. Experimental and Clinical Evidence
II. Triggers for Inflammation
III. Role in Development and Progression of Atherosclerosis
IV. ACS
V. Inflammatory Markers for Diagnosis and Prognosis
VI. Diagnostic and Therapeutic Implications


Normal Vessel
Endothelium
Lumen
Smooth
Muscle
Cells
Internal
Elastic
Lamina



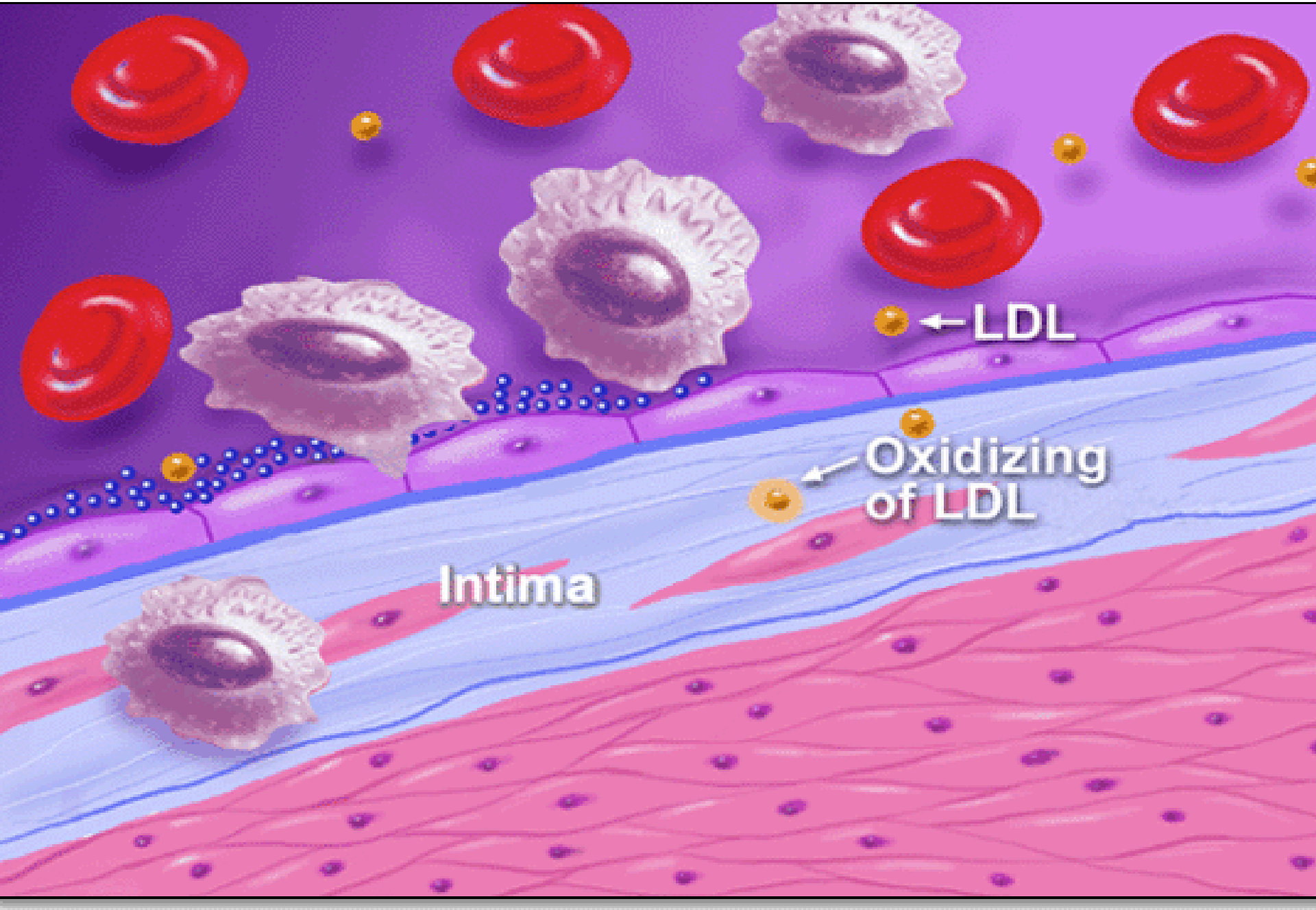
JACC. 2003. Vol. 42; pg. 1149

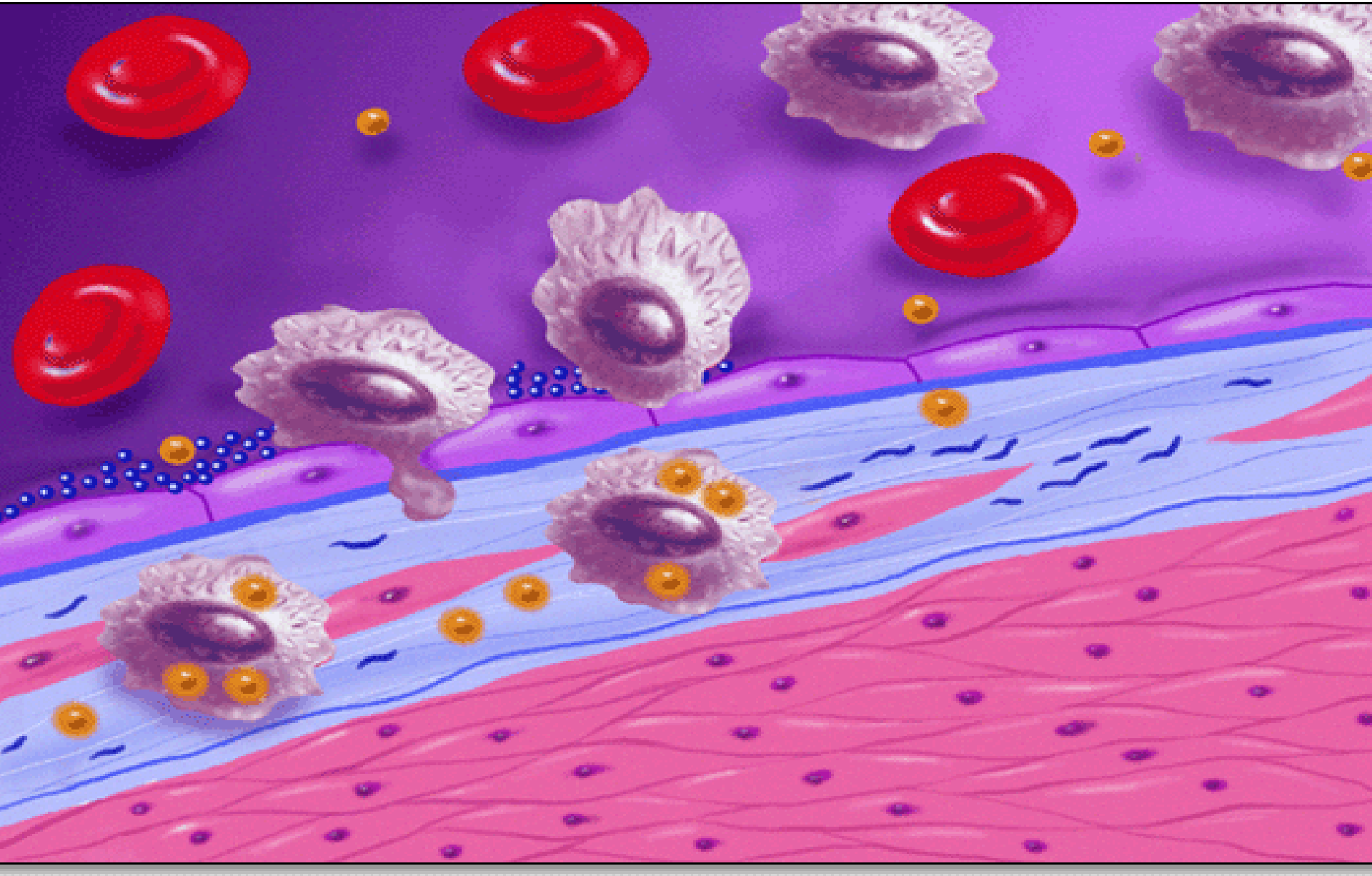
Evidence for Inflammation

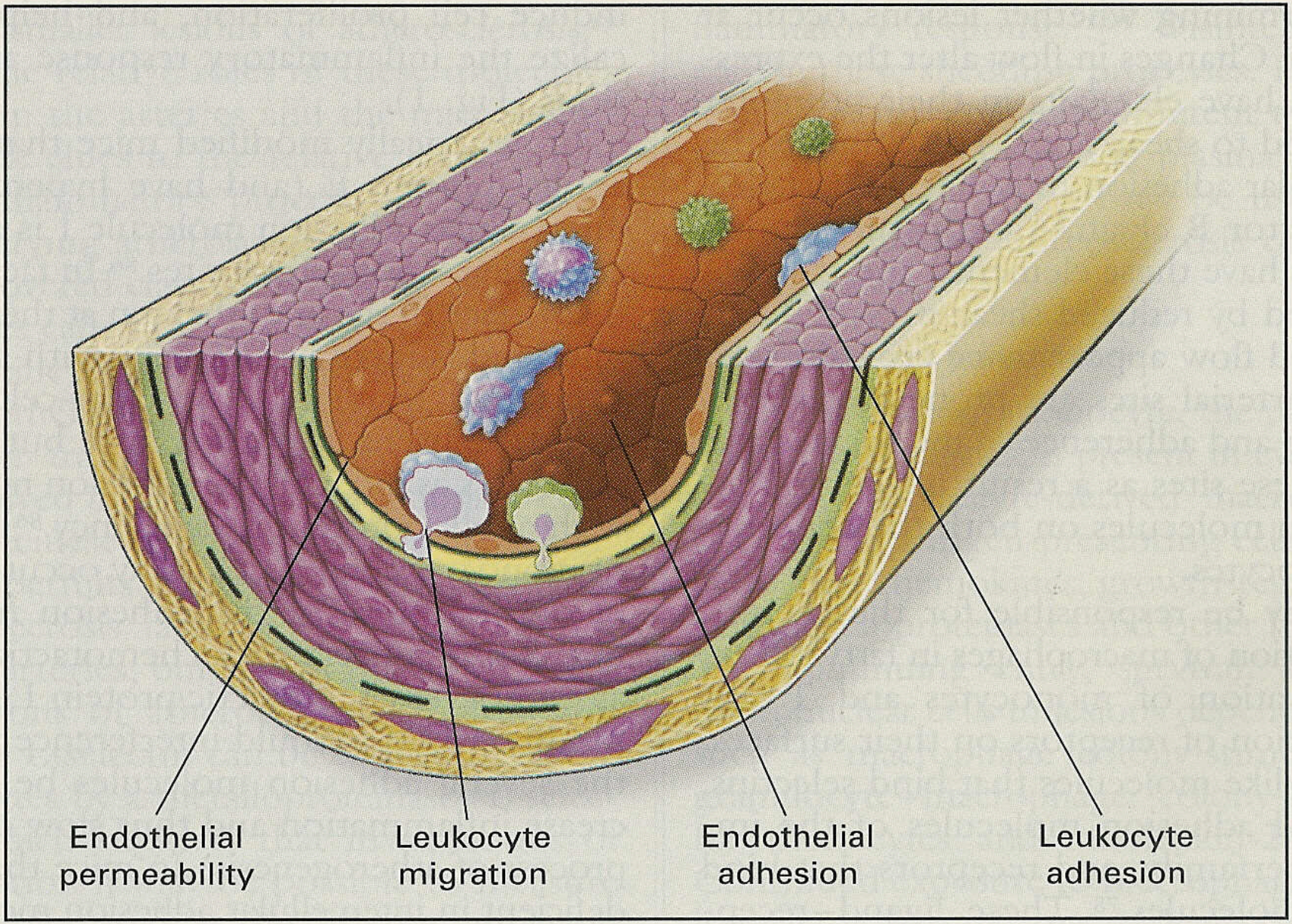
- Leukocytes in Earliest Lesions
- Expression of Adhesion Molecules
  - **VCAM**
  - **ICAM**

  Bind Monocytes and T-Cells
- Chemoattractant Molecules (MCP-I)
  - **Migration of Monocytes and T-Cells to Intima**


LDL
Oxidizing
of LDL
Intima

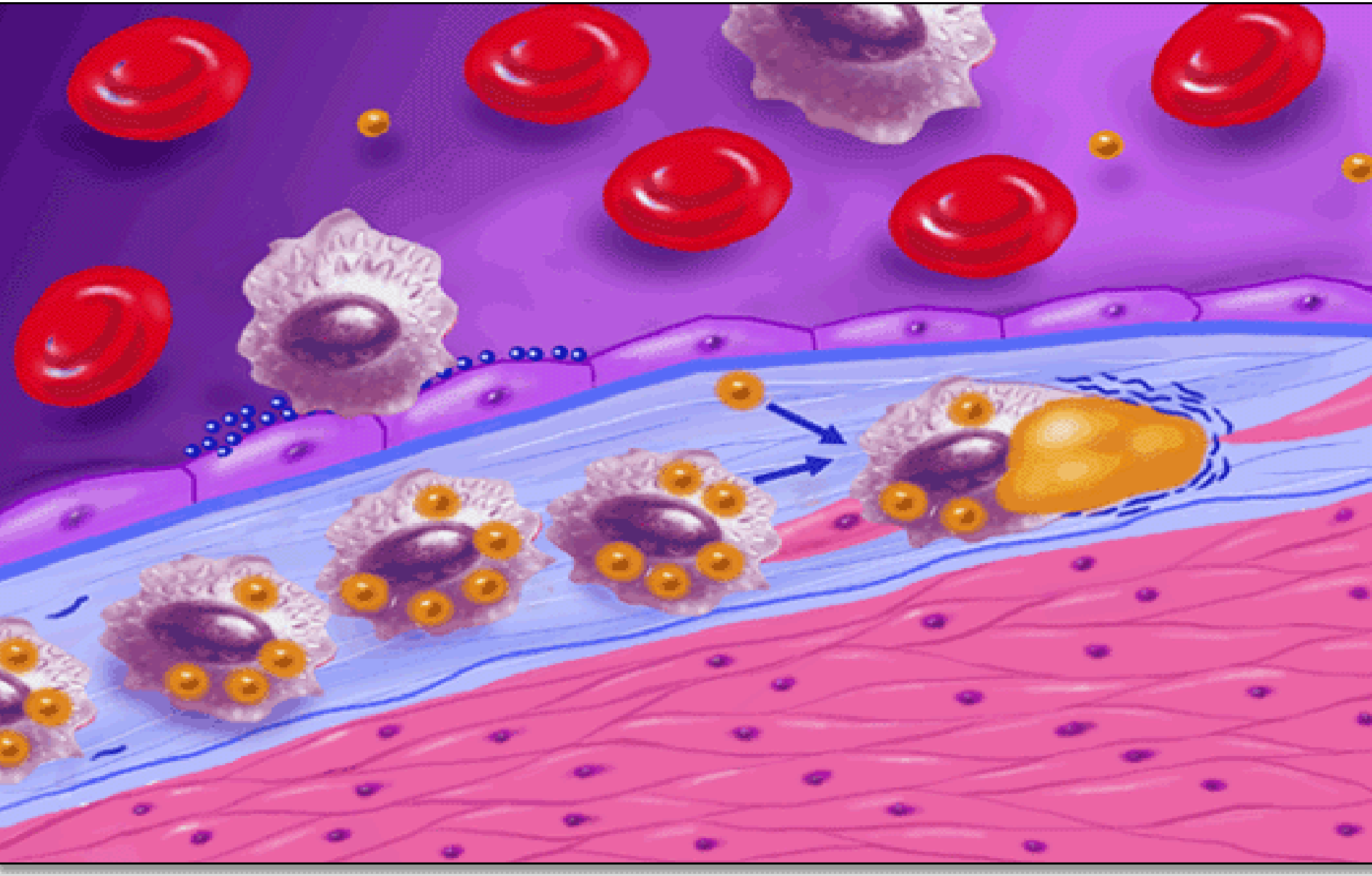


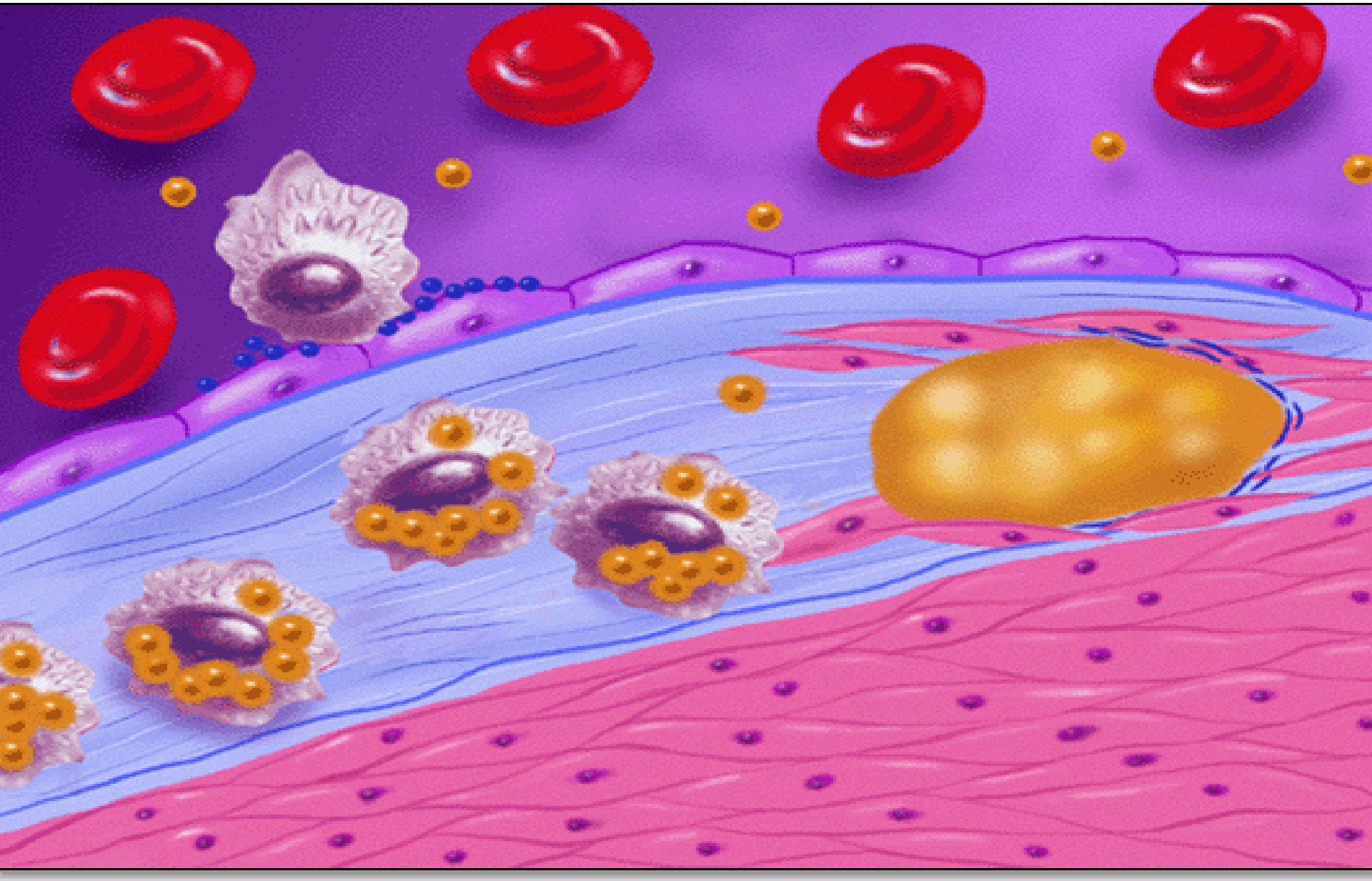


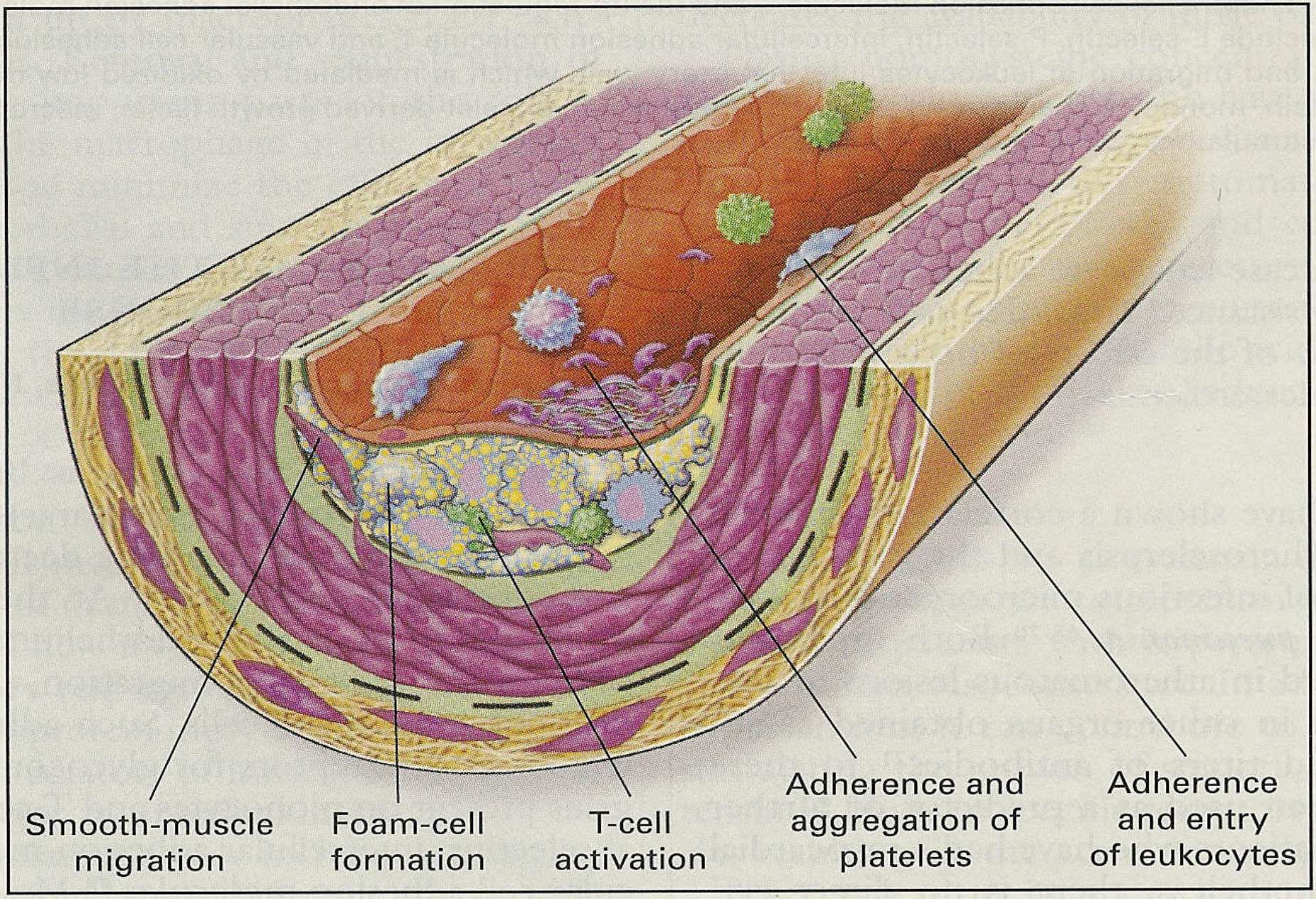
NEJM. 1999. Vol. 340; pg. 117

Evidence for Inflammation

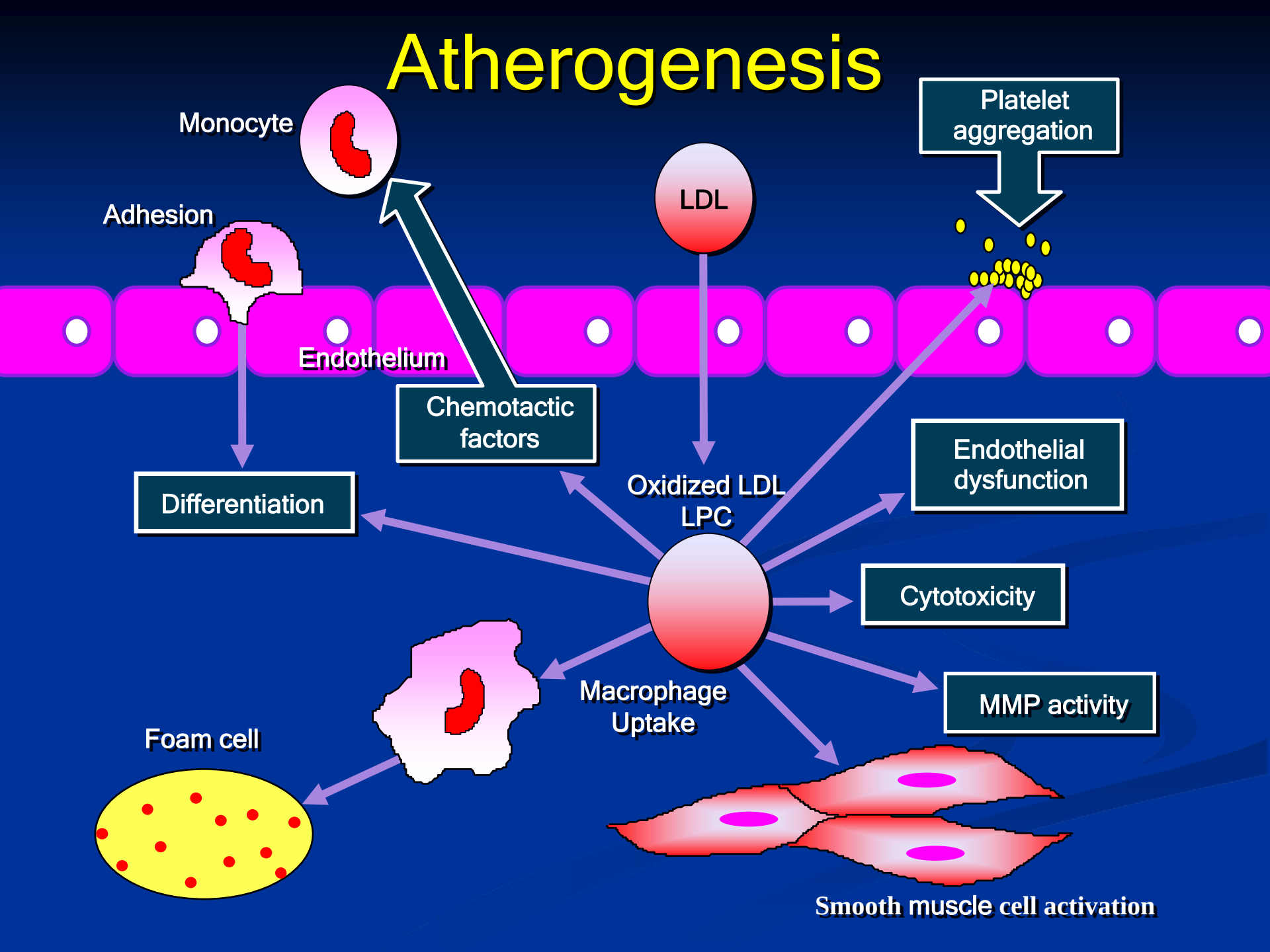
- Macrophage Colony Stimulating Factor (MCSF)
  - **Monocytes Transform into Macrophages**
  - **Macrophages Express Receptors to Scavenge Oxidized LDL (Foam Cells)**
- **Cytokines Secreted by T-Cells**
  - **Stimulate Macrophages, Endothelial Cells and Smooth Muscle Cells to Replicate and Elaborate Extracellular Matrix**



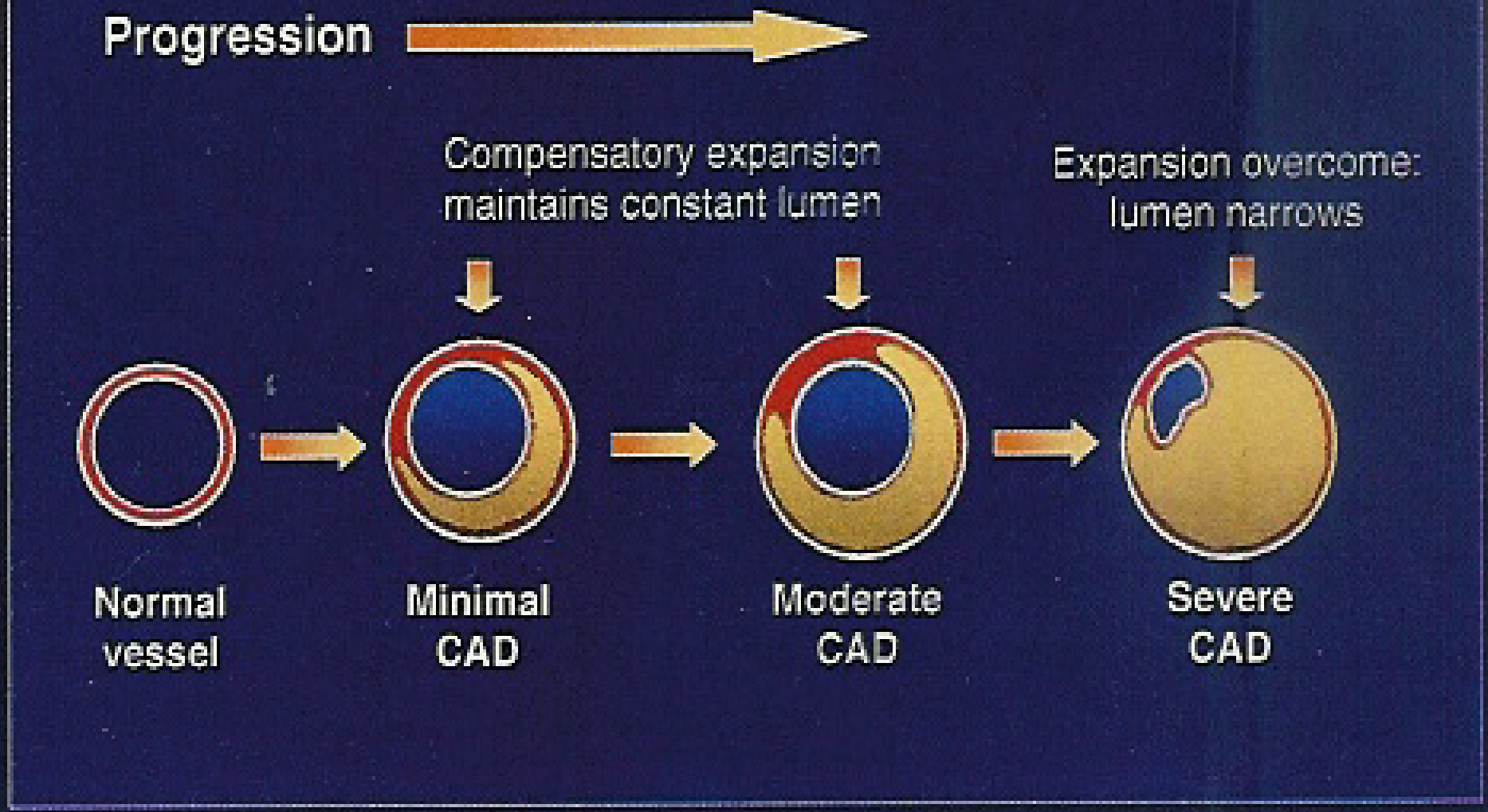




NEJM. 1999. Vol. 340; pg. 118


Atherogenesis
Monocyte
Adhesion
LDL
Platelet aggregation
Endothelium
Chemotactic factors
Differentiation
Oxidized LDL
LPC
Endothelial dysfunction
Cytotoxicity
Macrophage Uptake
MMP activity
Foam cell
Smooth muscle cell activation

Atheromata first grow outward: compensatory enlargement or positive remodeling



Adapted from Glagov et al. *N Engl J Med.* 1987;316:1371-1375.

Inflammation Triggers

- Oxidized LDL
  - Expression of :
    - Adhesion Molecules
    - Cytokines (Interleukins TNF)
    - Activate T-Cells
    - Foam Cells
    - Reactive O_2 Species (ROS)
- HBP ⇒ ⇑ Angiotensin II
  - Elicits Production of ROS
  - Stimulates Release of
  - IL-6, MCP by SMC's
  - VCAM on Endothelial Cells
  - SMC Hypertrophy

Inflammation Triggers

- DM
  - Cytokines
  - ROS
- Obesity
  - Insulin Resistance
  - Adipose Tissue Produces Cytokines
  - Free Fatty Acids ROS
- Smoking
  - $O_2^{\circ -}$ (ROS)
- Infections
  - Chlamydia

Endotoxin in Plaques

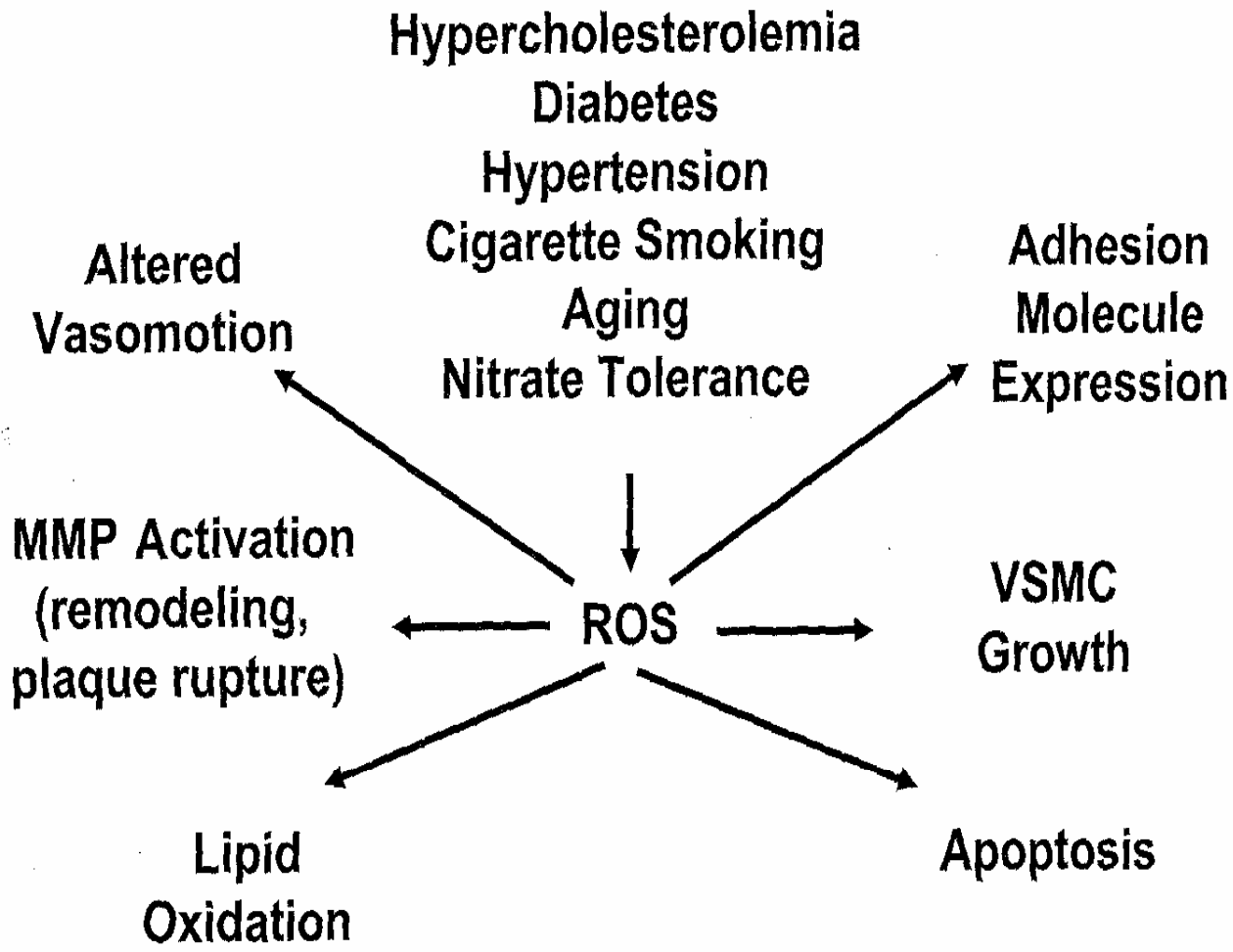


FIGURE 1. Roles of reactive oxygen species (ROS) in vascular disease. MMP = matrix metalloproteinase; VSMC = vascular smooth muscle cell.

American Journal of Cardiology. 2003. Vol. 91, pg. 8A

Development and Progression of Atherosclerosis

Each Lesion is Different Stage of Inflammation

- **Trigger Induced Endothelial Dysfunction**

- **Fatty Streak – Earliest Lesion**

(Monoctye Derived Macrophages / Foam Cells and T Lymphocytes)

[Ongoing Insult] **[Resolution]**

- **Altered Homeostatic Properties**
  - **Increased Permeability**
  - **Leukocyte and Platelet Adhesion**
  - **Expression of Vasoactive Molecules**
  - **Procoagulant Properties**

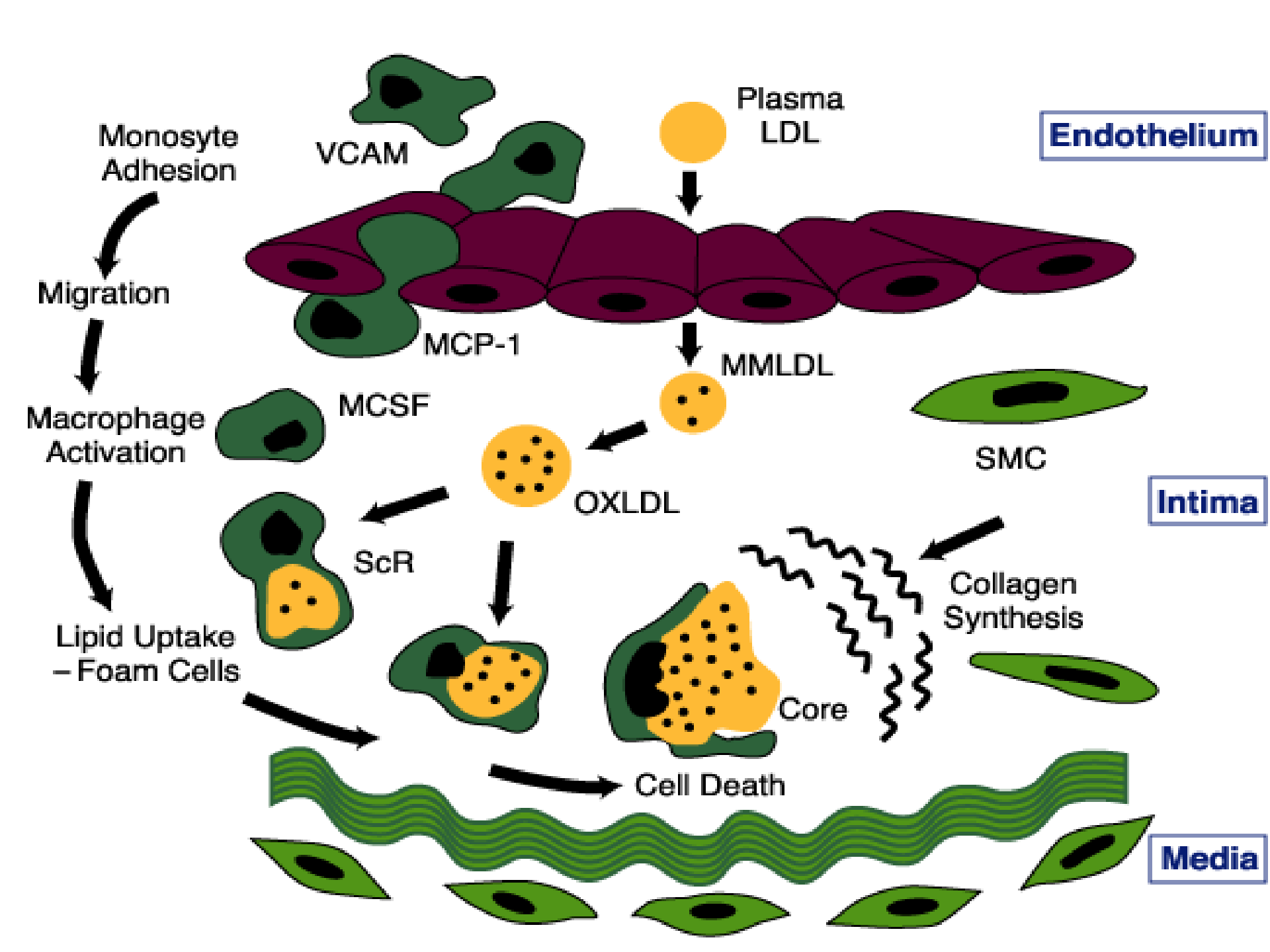
[Ongoing Insult] **[Resolution]**

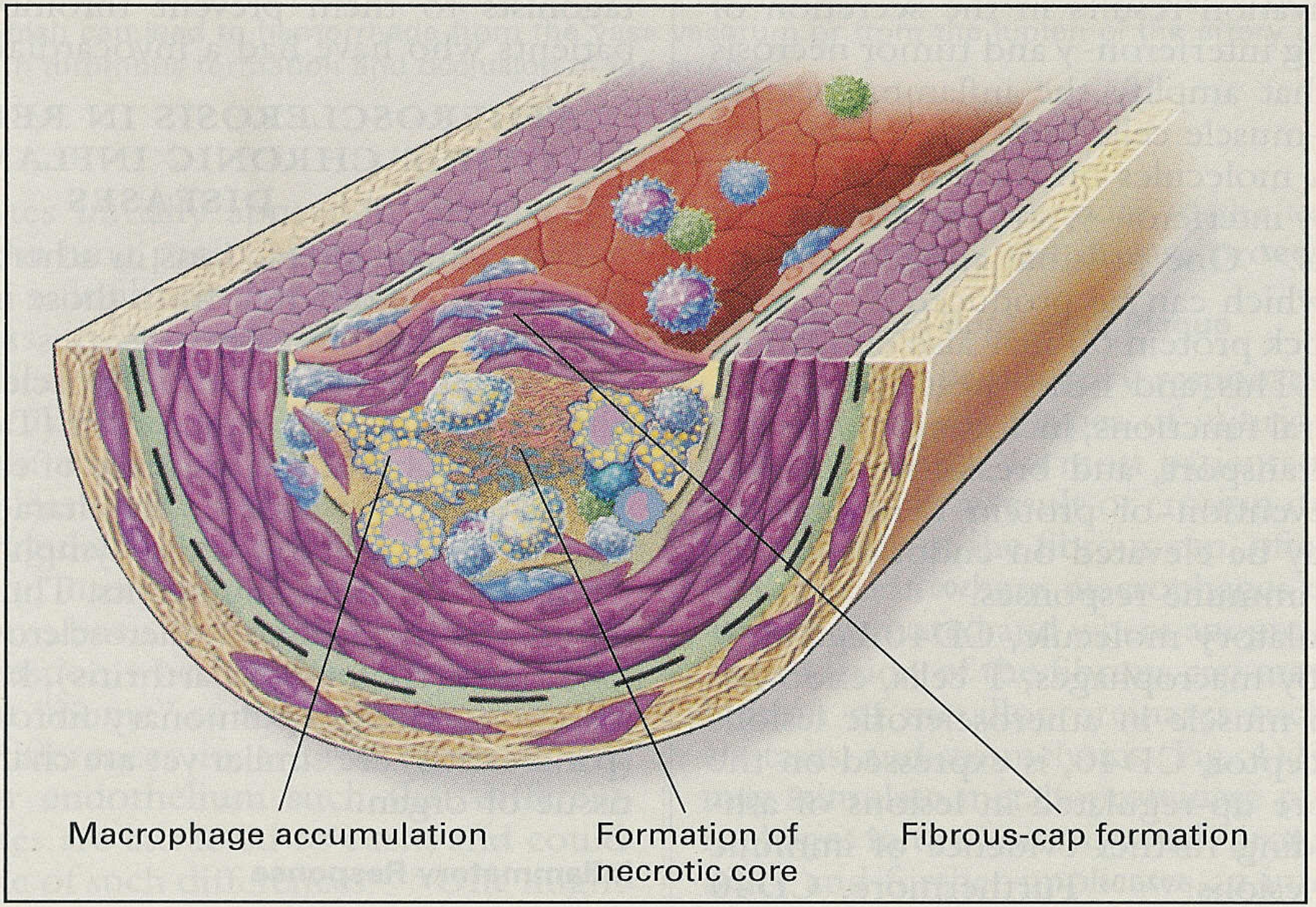
Development and Progression of Atherosclerosis

- Migration and Proliferation SMC's
- Fibrous CAP
- Remodeling and Dilitation of Vessel and Maintainence of Lumen Diameter

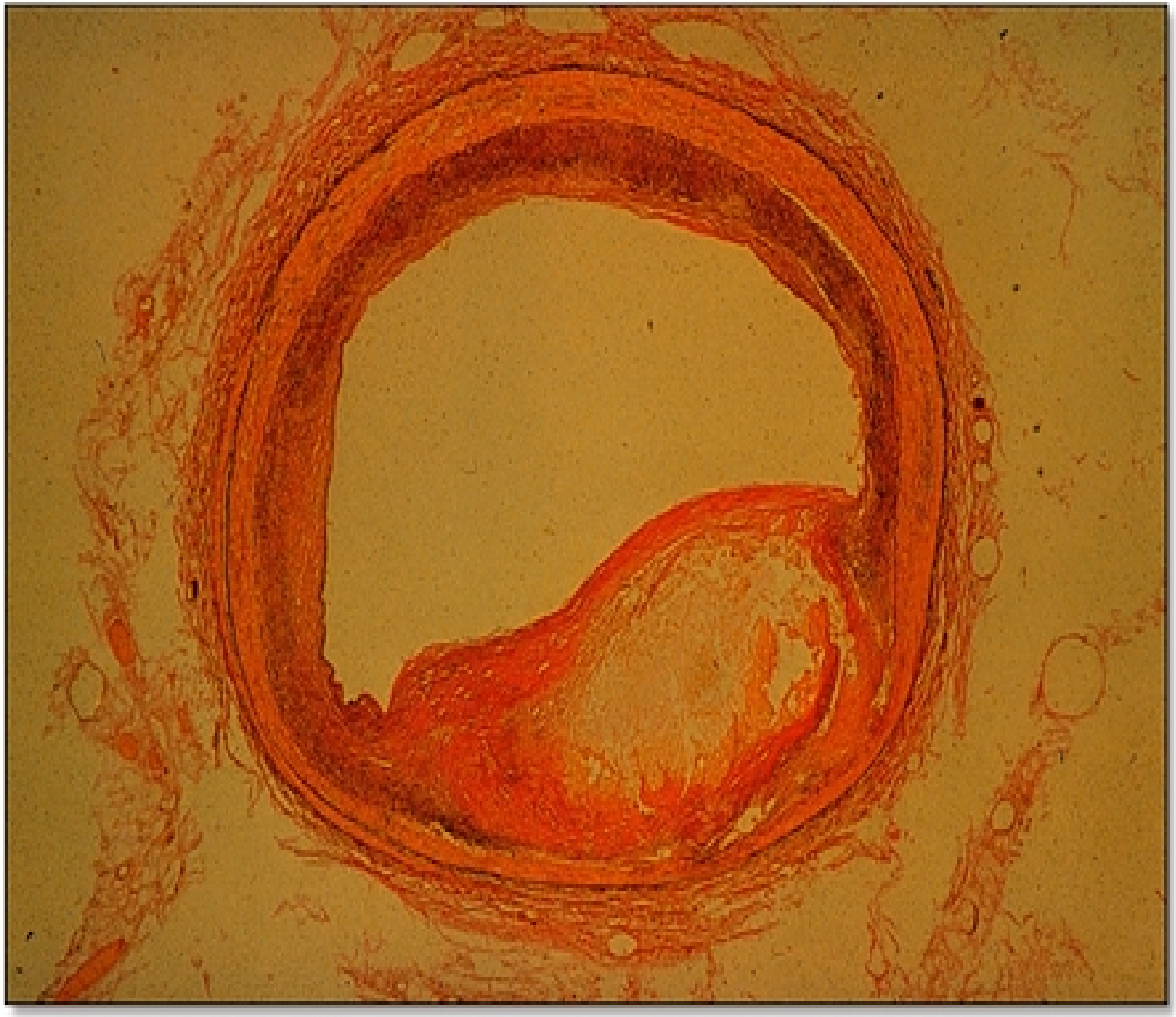
[Ongoing Insult]  [Resolution]

- Migration and Activation of Macrophages and T Cells
- Release of Cytokines, Growth Factor


Monosyte Adhesion
VCAM
Plasma LDL
Endothelium
Migration
MCP-1
MMLDL
Macrophage Activation
MCSF
SMC
OXLDL
Intima
ScR
Collagen Synthesis
Lipid Uptake – Foam Cells
Core
Cell Death
Media



NEJM. 1999. Vol. 340; pg. 119



Progression of Lesions and Acute Coronary Syndromes

Recurrent Cycles of Insult

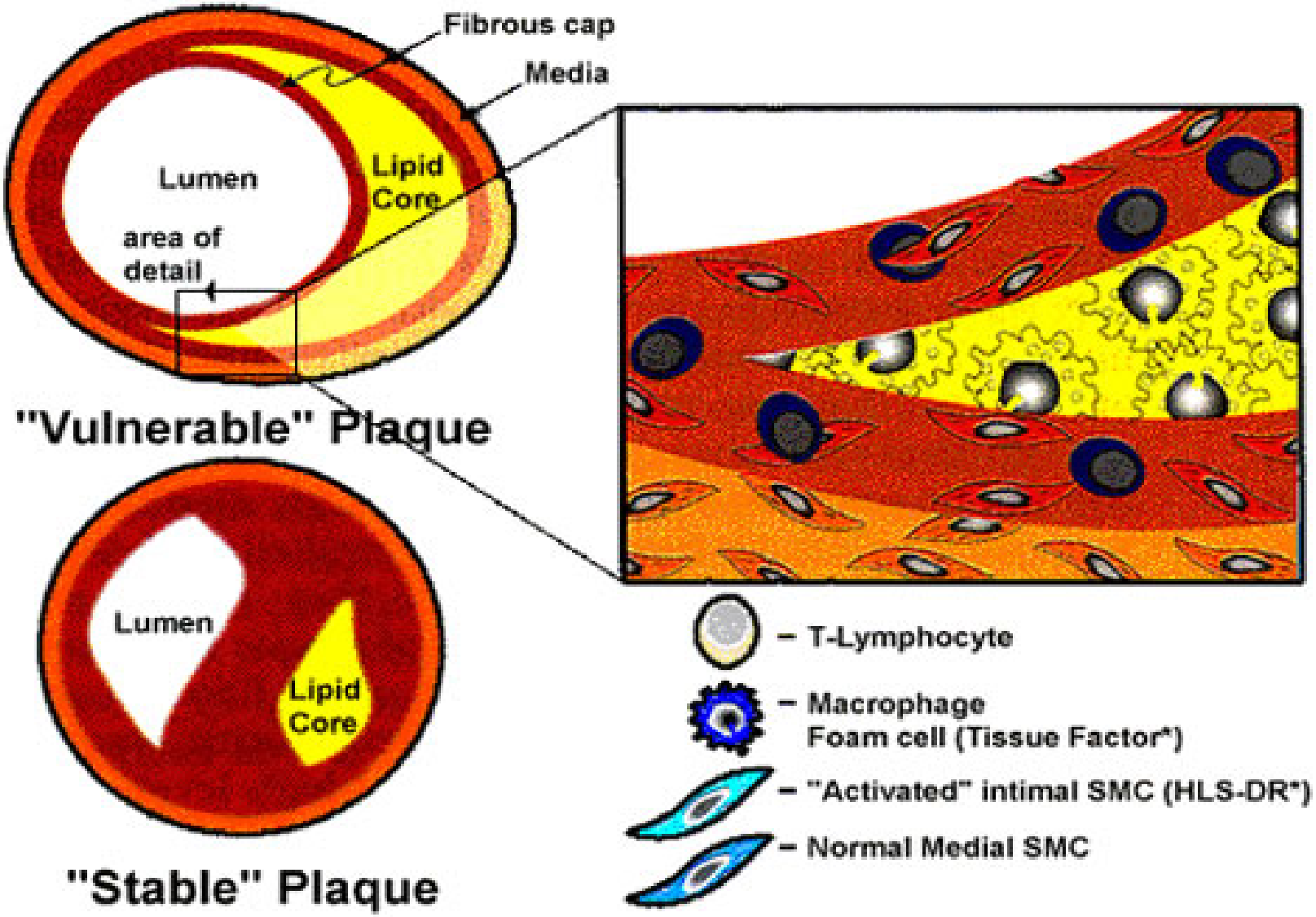
- Recruitment of more Leukocytes
- Migration and Proliferation SMC's
- Deposition of Extracellular Matrix
- Lesion Intrudes into Lumen

Focal Necrosis 2 Release of Enzymes

Fibrous Cap Overlying a Core of Lipid Necrotic Tissue

Vulnerable Plaque

Comparison of Vulnerable and Stable Plaques



Progression of Lesions and Acute Coronary Syndromes

Vulnerable Plaque

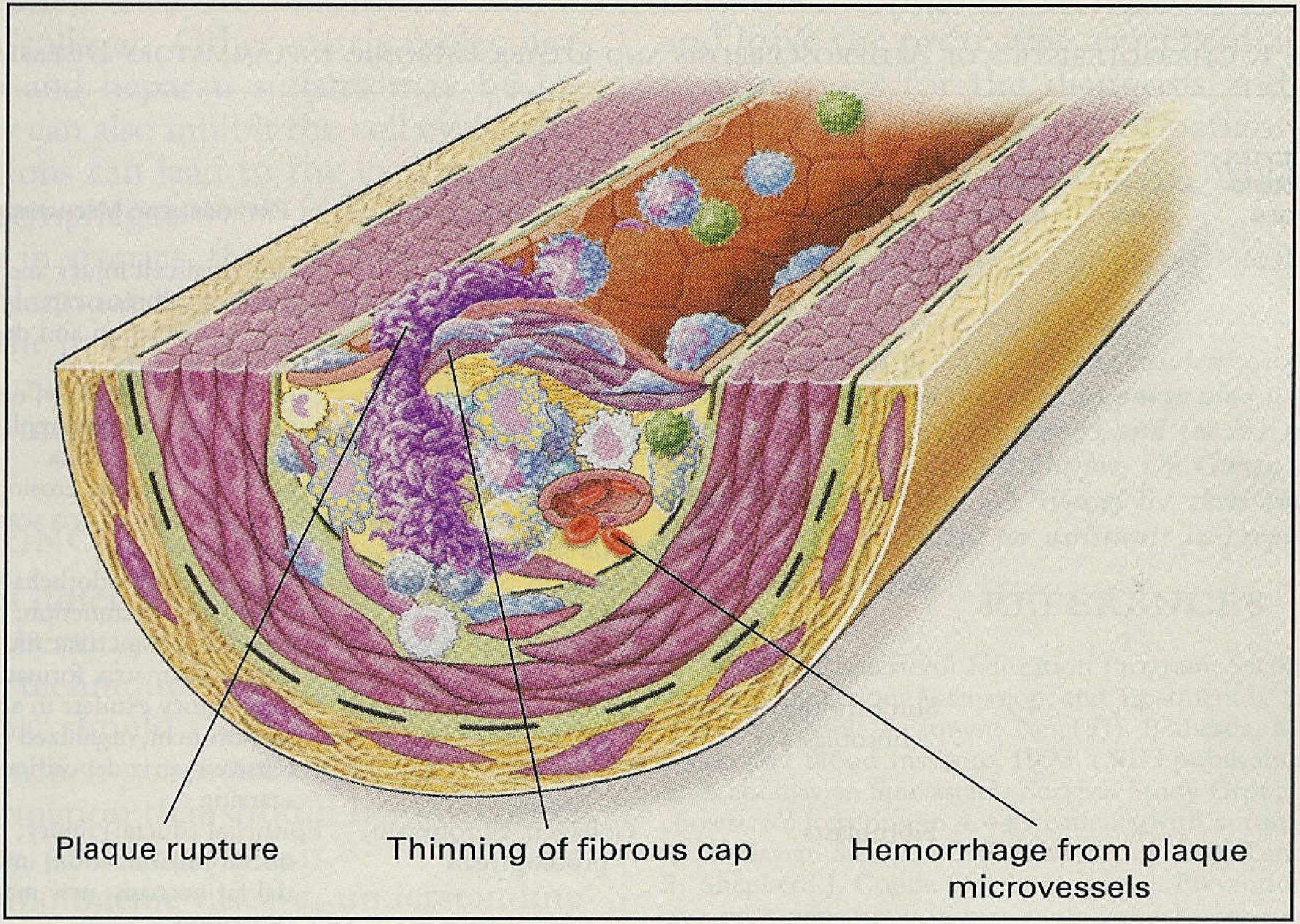
Plaque Rupture

Levels of Fibrinogen

Plasminogen Activator Inhibitor

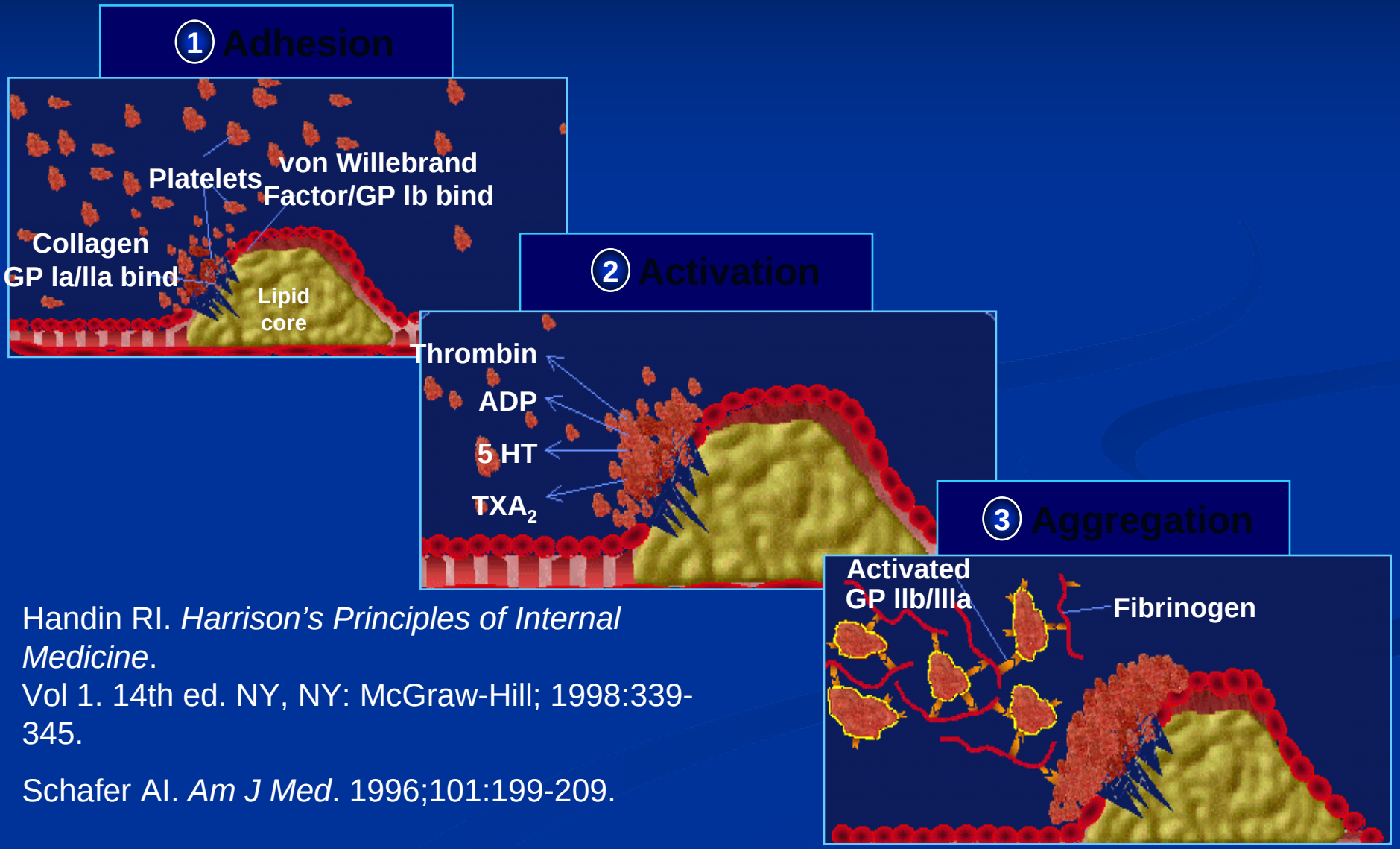
Activated Platelets

Clot



NEJM. 1999. Vol. 340; pg. 121

Platelet Cascade in Thrombus Formation



Handin RI. *Harrison's Principles of Internal Medicine*. Vol 1. 14th ed. NY, NY: McGraw-Hill; 1998:339-345.

Schafer AI. *Am J Med*. 1996;101:199-209.

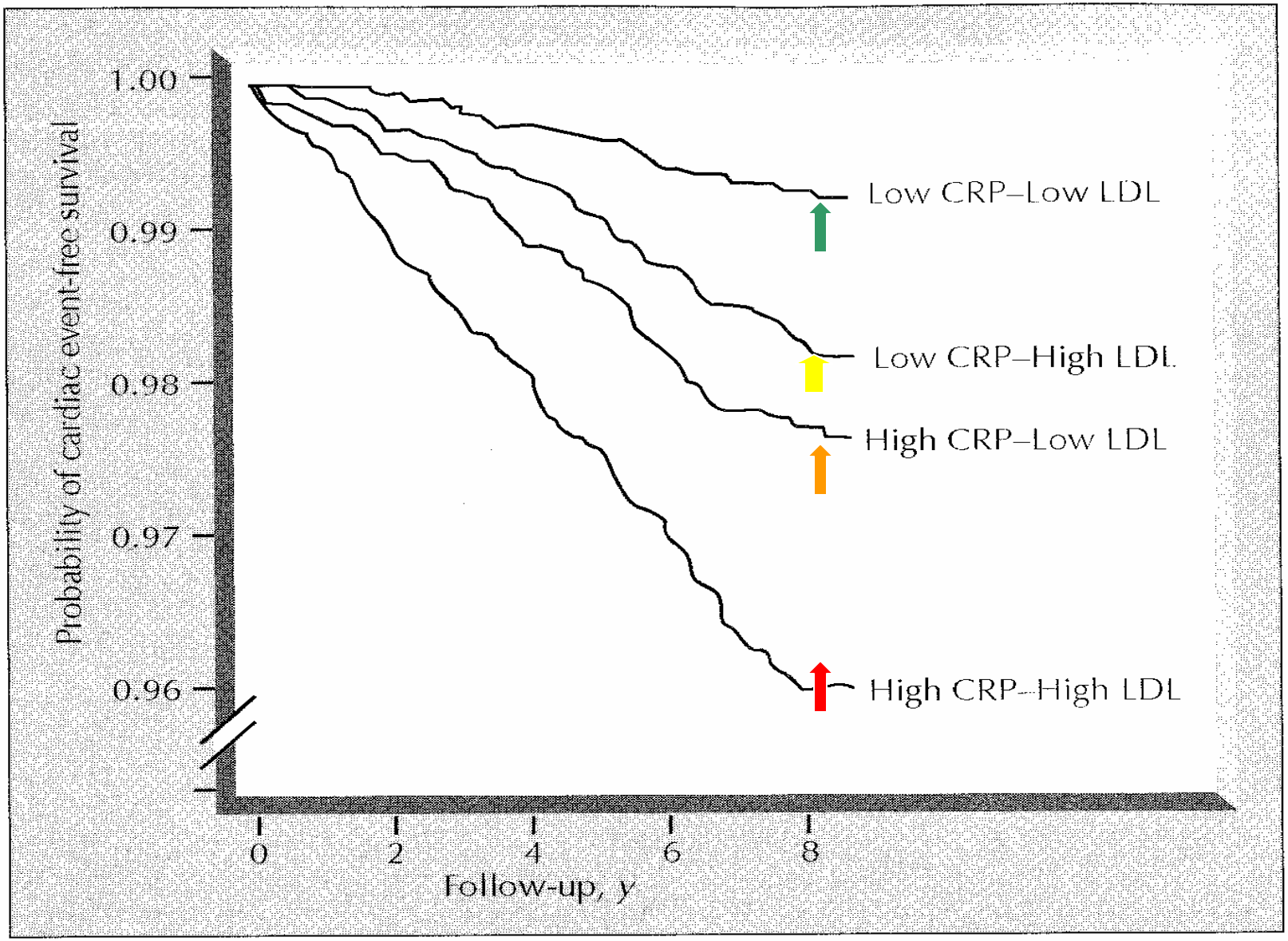
Use of Markers of Inflammation for Diagnosis and Prognosis

C-Reactive Protein (CRP)

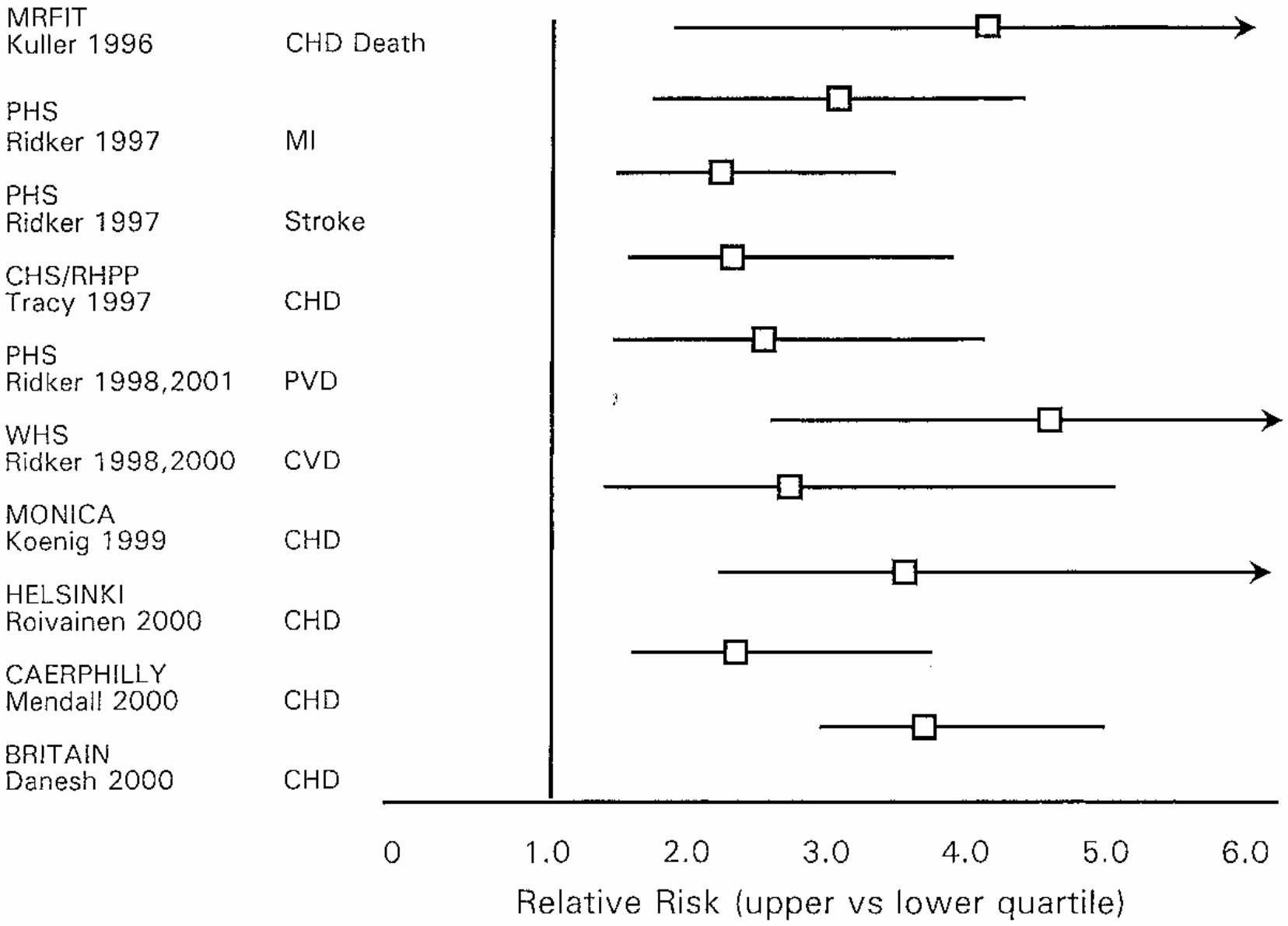
- Produced in Liver and Adipose Tissue in Response to Interleukin – 6
- Marker of Inflammation (and More)
- Up Regulates ICAM and VCAM
- Induces Release MCP
- Differentiation of Monocytes to Macrophages and Foam Cells

CRP as a Marker

- Marked Elevation with Systemic Inflammation (>15 mg/l)
  - Rheumatoid Arthritis
  - Endocarditis
  - Inflammatory Bowel Disease
  - Trauma
- Values < 10mg/l Reliable Predictors
- Low Degree of Variability in Any One Individual
- Higher Levels Correlate with Increased Risk Future CVD (MRFIT/PHS/MONICA)
  - MI
  - CVA
  - PVD
  - SCD
- Stronger Predictor f Events than LDL
- Known CVD, CRP Predicts (CARE)
  - Death
  - Recurrent Vascular Events



NEJM. 2002. Vol. 347; pg. 1558



Circulation. Vol. 105; pg. 1140

Therapeutic Implications
PHS

- Aspirin Reduced Risk for MI

  Most in Patients with Highest CRP

  (And Therefore *Most* Inflammation)

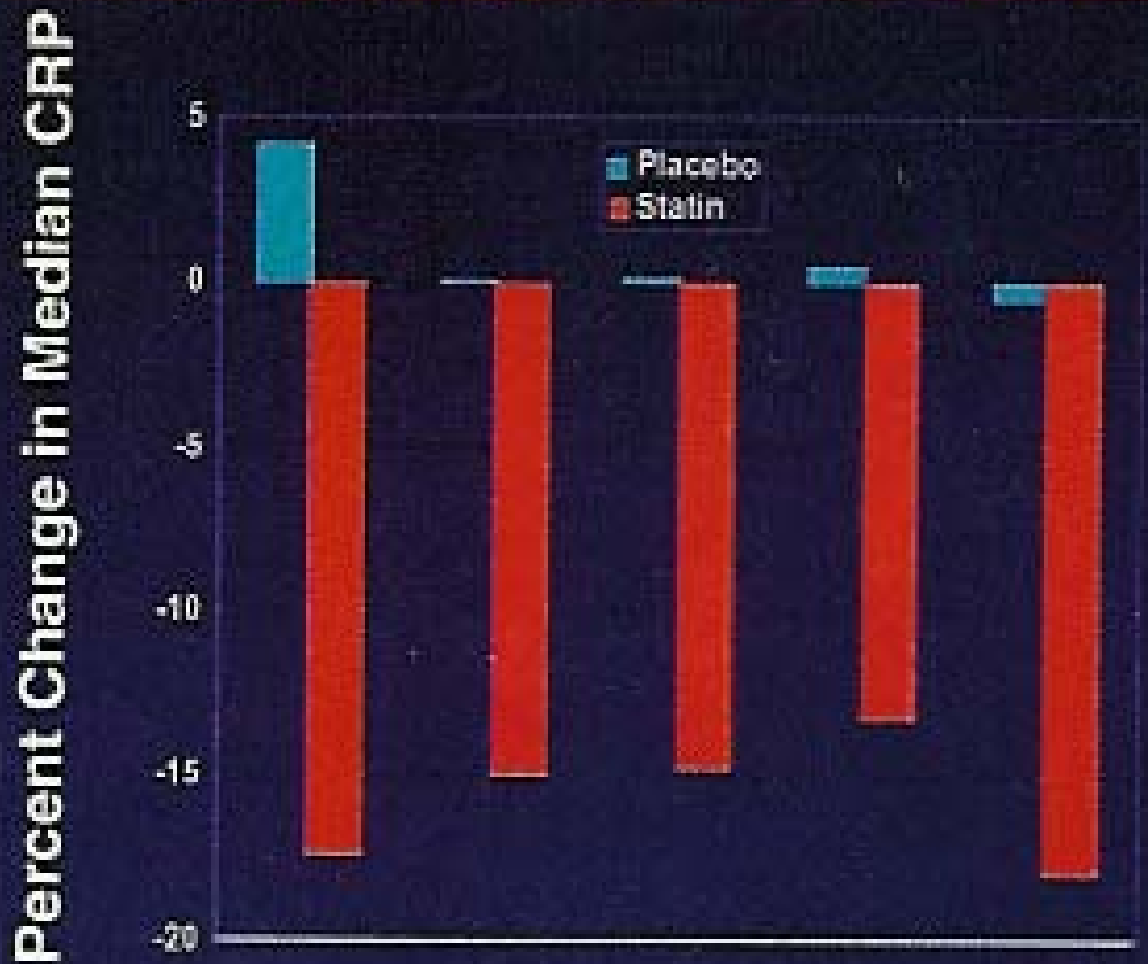
  SUGGESTS:

- Anti-Inflammatory Properties of ASA may Contribute to Prevention of CVD

CARE
(Cholesterol And Recurrent Events)

- 400 Patients with Prior MI
- Measure CRP
- Monitor for Second MI or Death
  - Baseline CRP Elevations Correlated with Subequent Event (Higher CRP ⇨ Higher Risk)
- Pravastatin Reduced Risk for Second Event Most in Patients with Highest CRP
- Significant Fall in CRP (Post-Rx)

Statin Therapy decreases CRP

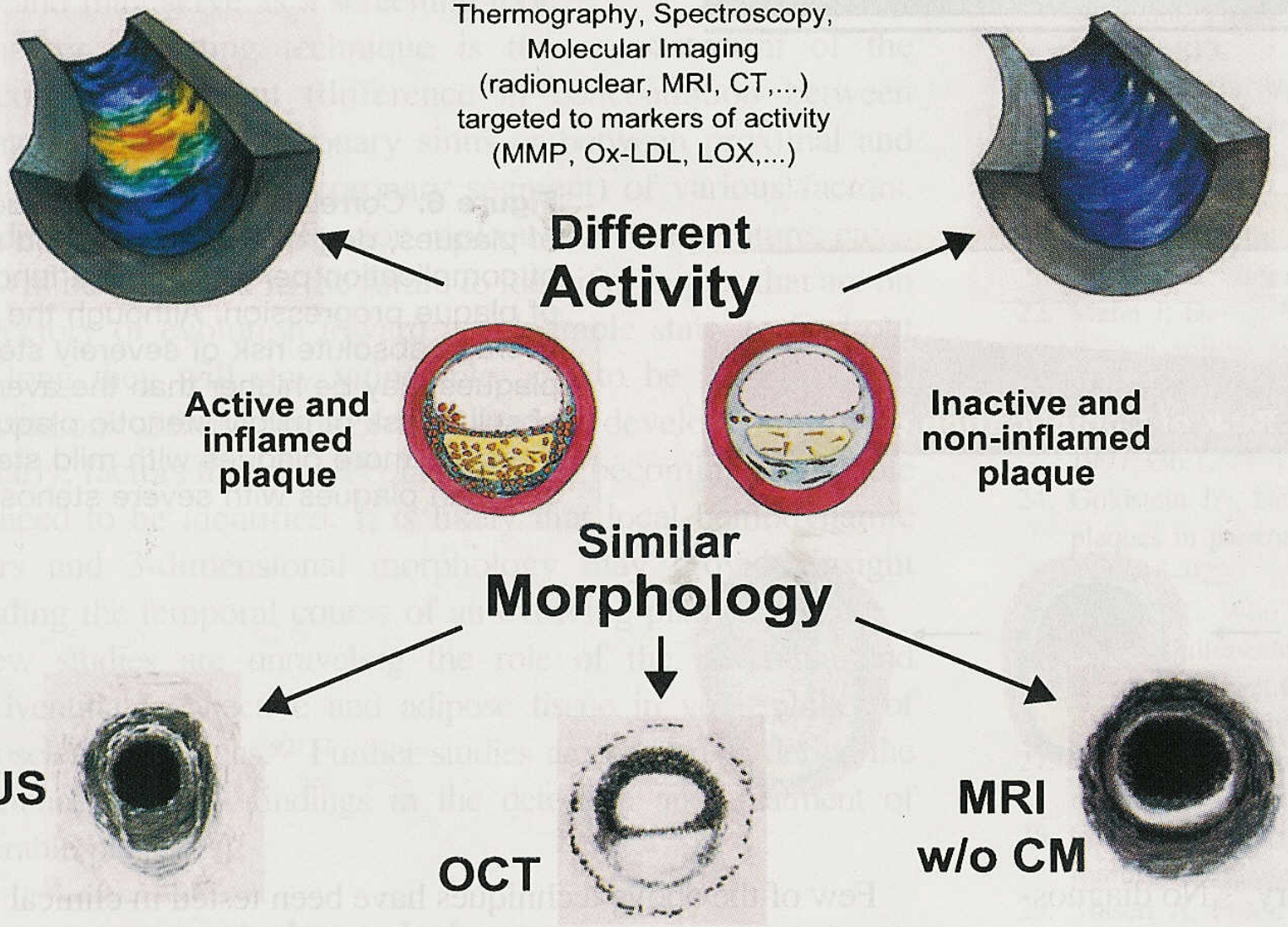


Ridker, 2001

Observations Suggest

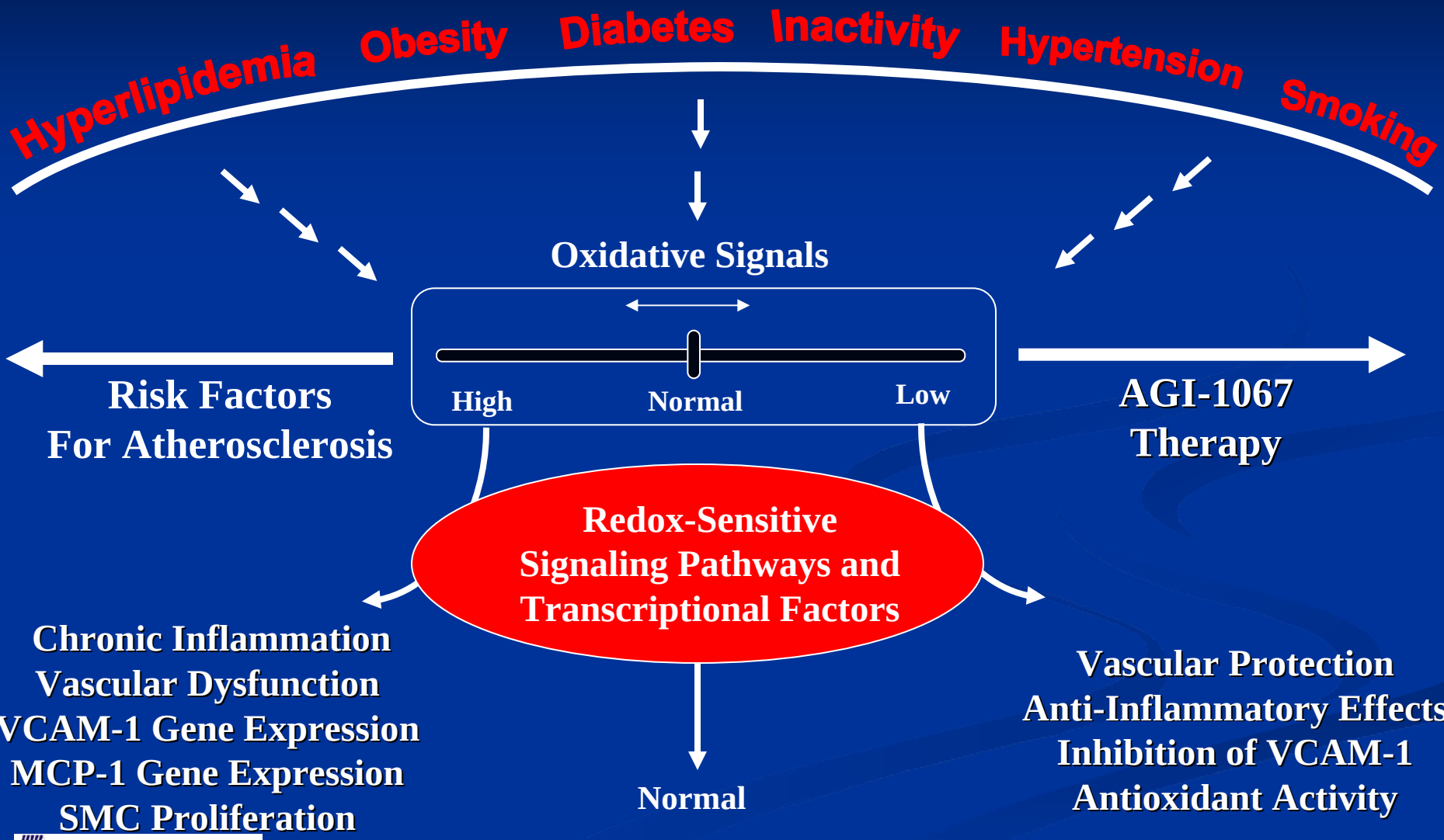
- Increased Risk Associated with Evidence for Inflammation may be Modifiable by Drug Intervention
- CRP may Prove Useful for Targeting Specific Therapy
- Fall in CRP Might Permit Assessment of Efficacy of Therapy (and Reduction in Risk)

Morphology vs. Activity Imaging



Circulation. 2003 Vol. 108, pg 1669

V-Protectant: Novel Therapeutic for the Treatment of Atherosclerosis

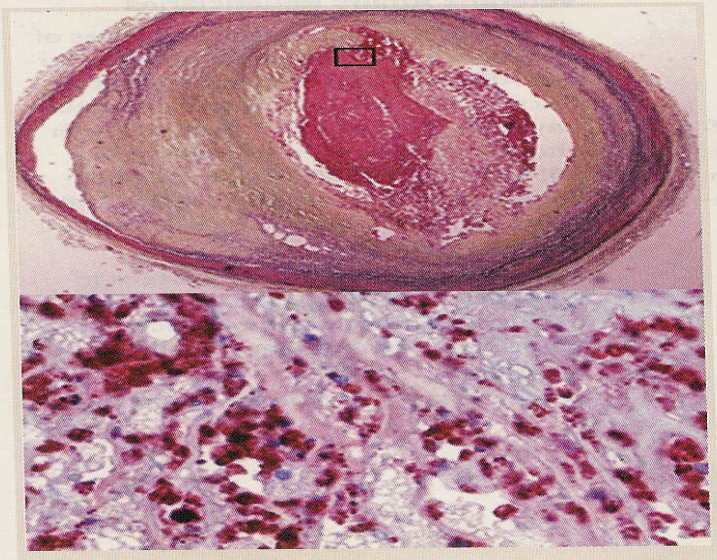


This Week in the Journal

OCTOBER 23, 2003

ORIGINAL ARTICLE

Prognostic Value of Myeloperoxidase in Acute Coronary Syndromes



Myeloperoxidase Staining

Inflammation appears to have a key role in acute coronary syndromes. Myeloperoxidase, an enzyme that generates reactive oxygen species, is released from leukocytes on activation, and plasma levels of myeloperoxidase may serve as a marker of inflammation. In this study, plasma myeloperoxidase levels were found to be predictive of subsequent coronary events in patients with chest pain, even when patients were initially negative for troponin T.

Plasma myeloperoxidase levels may be of use in risk stratification among patients with suspected acute coronary syndromes.

SEE P. 1595; PERSPECTIVE, P. 1587

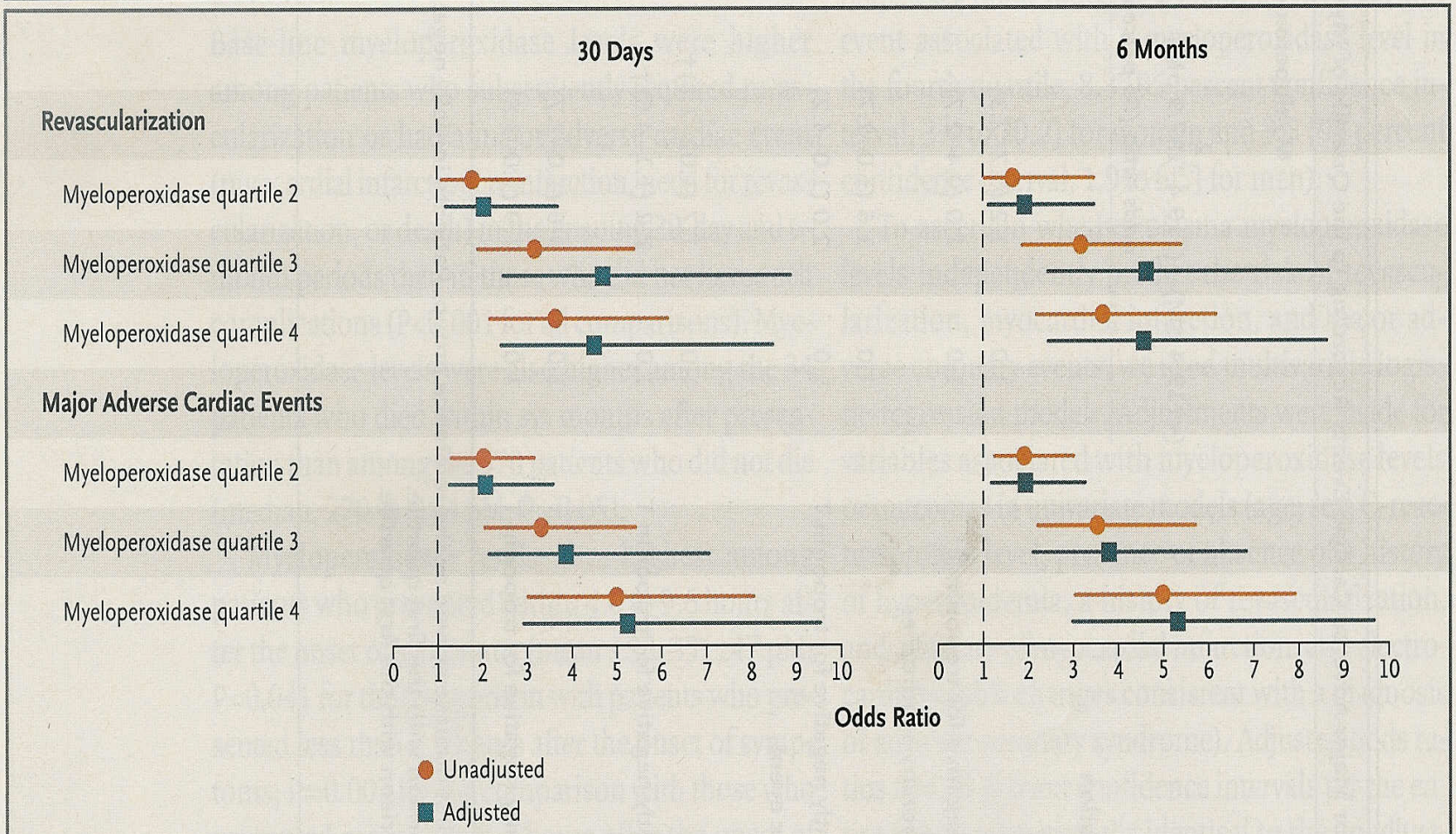


Figure 1. Risks of Revascularization and Major Adverse Cardiac Events among Patients Who Were Consistently Negative for Troponin T, According to Base-Line Myeloperoxidase Levels.

Odds ratios and 95 percent confidence intervals are shown. Adjusted odds ratios were adjusted for age; sex; C-reactive protein level; presence or absence of a history of hyperlipidemia, revascularization, or myocardial infarction; and electrocardiographic changes consistent with a diagnosis of acute coronary syndromes. For each comparison, the first quartile served as the reference group.

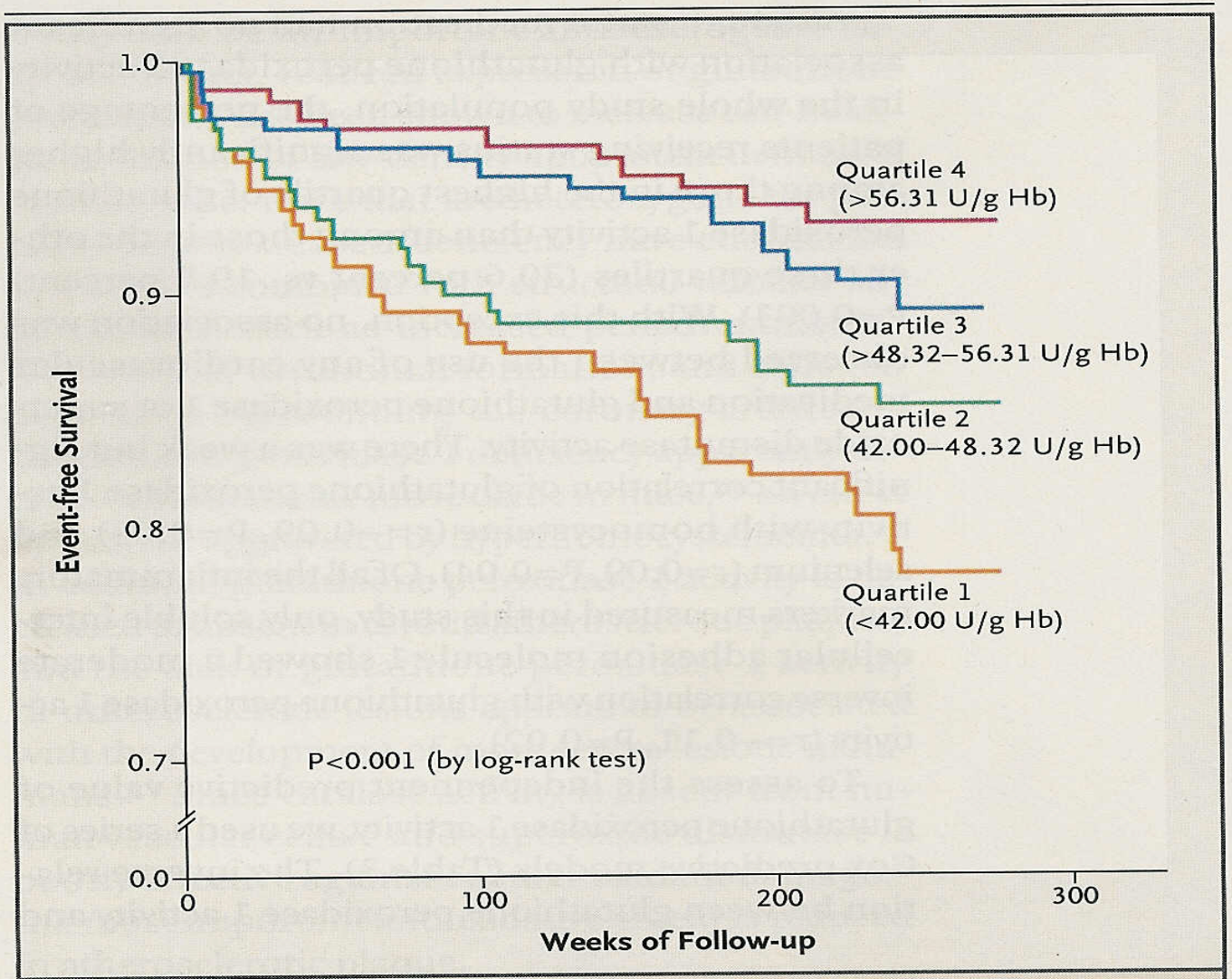


Figure 1. Kaplan–Meier Curves Showing Cardiovascular Events According to Quartile of Glutathione Peroxidase 1 Activity.

The numbers of cardiovascular events were 33, 23, 16, and 11 in quartiles 1, 2, 3, and 4, respectively. Glutathione peroxidase 1 activity is shown in units per gram of hemoglobin.

ORIGINAL ARTICLE

Use of Multiple Biomarkers to Improve the Prediction of Death from Cardiovascular Causes

Björn Zethelius, M.D., Ph.D., Lars Berglund, M.Sc., Johan Sundström, M.D., Ph.D., Erik Ingelsson, M.D., Ph.D., Samar Basu, M.Sc., Ph.D., Anders Larsson M.D., Ph.D., Per Venge, M.D., Ph.D., and Johan Ärnlöv, M.D., Ph.D.

ABSTRACT

BACKGROUND

The incremental usefulness of adding multiple biomarkers from different disease pathways for predicting the risk of death from cardiovascular causes has not, to our knowledge, been evaluated among the elderly.

METHODS

We used data from the Uppsala Longitudinal Study of Adult Men (ULSAM), a community-based cohort of elderly men, to investigate whether a combination of biomarkers that reflect myocardial cell damage, left ventricular dysfunction, renal failure, and inflammation (troponin I, N-terminal pro–brain natriuretic peptide, cystatin C, and C-reactive protein, respectively) improved the risk stratification of a person beyond an assessment that was based on the established risk factors for cardiovascular disease (age, systolic blood pressure, use or nonuse of antihypertensive treatment, total cholesterol, high-density lipoprotein cholesterol, use or nonuse of lipid-lowering treatment, presence or absence of diabetes, smoking status, and body-mass index).

RESULTS

During follow-up (median, 10.0 years), 315 of the 1135 participants in our study (mean age, 71 years at baseline) died; 136 deaths were the result of cardiovascular disease. In Cox proportional-hazards models adjusted for established risk factors, all of the biomarkers significantly predicted the risk of death from cardiovascular causes. The C statistic increased significantly when the four biomarkers were incorporated into a model with established risk factors, both in the whole cohort (C statistic with biomarkers vs. without biomarkers, 0.766 vs. 0.664; $P<0.001$) and in the group of 661 participants who did not have cardiovascular disease at baseline (0.748 vs. 0.688, $P=0.03$). The improvement in risk assessment remained strong when it was estimated by other statistical measures of model discrimination, calibration, and global fit.

CONCLUSIONS

Our data suggest that in elderly men with or without prevalent cardiovascular disease, the simultaneous addition of several biomarkers of cardiovascular and renal abnormalities substantially improves the risk stratification for death from cardiovascular causes beyond that of a model that is based only on established risk factors.

From the Department of Public Health and Caring Sciences/Geriatrics (B.Z., L.B., E.I., S.B., J.Ä.), Uppsala Clinical Research Center (L.B.), and the Department of Medical Sciences (J.S., A.L., P.V.), Uppsala University, Uppsala, Sweden. Address reprint requests to Dr. Ärnlöv at the Department of Public Health and Caring Sciences/Geriatrics, Uppsala Science Park, SE-75185 Uppsala, Sweden, or at johan.arnlov@pubcare.uu.se.

N Engl J Med 2008;358:2107-16.

Table 2: Inflammatory Markers Related to Coronary Disease

C-reactive protein
Cytokines
Interleukins (IL-1, IL-6)
Tumor necrosis factor-α
CD40 ligand
Lipoprotein-associated phospholipase A2
Matrix metalloproteinases
Pregnancy-associated plasma protein–A (PAPP-A)
Cellular adhesion molecules: ICAM-1, VCAM-1, selectins
Myeloperoxidase
Leukocytosis
Amyloid A

Adapted with permission from Murtagh BM, Anderson HV. Inflammation and atherosclerosis in acute coronary syndromes. Invasive Cardiol. 2004;16:377-384.

ICAM-1 = intracellular adhesion molecule 1; VCAM-1 = vascular adhesion molecule 1.

Table 2. Hazard Ratios for Death from All Causes and from Cardiovascular Causes, According to Biomarker Levels.*

Biomarker and Criterion	Death from Cardiovascular Causes		Death from All Causes	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Whole sample				
Troponin I				
1-SD increase	1.60 (1.41–1.82)	<0.001	1.36 (1.24–1.50)	<0.001
>0.021 μg/liter†	3.40 (2.31–5.00)	<0.001	2.28 (1.71–3.03)	<0.001
>0.035 μg/liter‡	4.08 (2.55–6.55)	<0.001	2.78 (1.92–4.02)	<0.001
NT-pro-BNP				
1-SD increase	2.03 (1.72–2.39)	<0.001	1.58 (1.41–1.76)	<0.001
≥386 ng/liter†	3.77 (2.60–5.46)	<0.001	2.53 (1.94–3.29)	<0.001
>309 ng/liter‡	4.10 (2.86–5.88)	<0.001	2.55 (1.98–3.28)	<0.001
Cystatin C				
1-SD increase	1.43 (1.22–1.66)	<0.001	1.31 (1.18–1.46)	<0.001
≥1.29 mg/liter†	2.01 (1.42–2.85)	<0.001	1.46 (1.16–1.85)	<0.001
>1.50 mg/liter‡	2.04 (1.34–3.12)	<0.001	1.90 (1.41–2.55)	<0.001
C-reactive protein				
1-SD increase	1.49 (1.24–1.78)	<0.001	1.41 (1.26–1.58)	<0.001
>3.0 mg/liter†	1.97 (1.39–2.78)	<0.001	1.64 (1.30–2.06)	<0.001
≥4.6 mg/liter‡	2.19 (1.53–3.12)	<0.001	1.92 (1.51–2.45)	<0.001
Participants without CVD at baseline				
Troponin I				
1-SD increase	1.77 (1.43–2.18)	<0.001	1.32 (1.13–1.56)	<0.001
>0.021 μg/liter†	2.85 (1.41–5.75)	0.003	1.60 (0.96–2.67)	0.07
>0.035 μg/liter‡	4.46 (1.93–10.28)	<0.001	1.82 (0.87–3.78)	0.11
NT-proBNP				
1-SD increase	2.16 (1.55–3.00)	<0.001	1.46 (1.18–1.80)	<0.001
≥386 ng/liter†	4.96 (2.48–9.92)	<0.001	2.60 (1.56–4.31)	<0.001
>309 ng/liter‡	4.69 (2.53–8.72)	<0.001	2.50 (1.60–3.89)	<0.001
Cystatin C				
1-SD increase	1.36 (1.05–1.77)	0.02	1.27 (1.08–1.50)	0.004
≥1.29 mg/liter†	2.02 (1.15–3.51)	0.01	1.59 (1.13–2.24)	0.008
>1.50 mg/liter‡	2.79 (1.44–5.41)	0.002	2.34 (1.50–3.65)	<0.001
C-reactive protein				
1-SD increase	1.49 (1.12–1.98)	0.006	1.35 (1.15–1.60)	<0.001
>3.0 mg/liter†	2.00 (1.16–3.44)	0.01	1.39 (0.99–1.94)	0.06
≥4.6 mg/liter‡	2.72 (1.56–4.73)	<0.001	1.79 (1.26–2.57)	<0.001

* Values were calculated with the use of multivariable Cox regression analysis. Data were adjusted for the following variables: age at baseline (continuous), systolic blood pressure (continuous), use or nonuse of antihypertensive treatment (binary), total cholesterol (continuous), high-density lipoprotein cholesterol (continuous), use or nonuse of lipid-lowering treatment (binary), presence or absence of diabetes (binary), smoking status (binary), and body-mass index (continuous). CVD denotes cardiovascular disease, and NT-pro-BNP N-terminal pro–brain natriuretic peptide.
† This is the cutoff point that has been suggested in the literature.
‡ This cutoff point has been identified for optimized discrimination in the present study.

Table 4. Comparison of Exercise Testing and Add-Ons or Other Test Modalities

Grouping	No. of Studies	Total No. of Patients	Sensitivity, %	Specificity, %	Predictive Accuracy, %
Meta-analysis of standard exercise ECG	147	24 047	68	77	73
Excluding MI patients	41	11 691	67	74	69
Limiting workup bias	2	2350	50	90	69
Meta-analysis of exercise test scores	24	11 788			80
Perfusion scintigraphy	2	28 751	89	80	89
Exercise echocardiography	58	5000	85	79	83
Nonexercise stress tests					
Pharmacological stress scintigraphy	11	<1000	85	91	87
Dobutamine echocardiography	5	<1000	88	84	86
EBCT	16	3683	91	49	70

MI indicates myocardial infarction.

Diagnosis

Test Your Knowledge | Normal Lab Reference

The first step in the diagnosis of CAD is to estimate the pretest probability based on known cardiovascular risk factors and symptoms. A simple estimate of the pretest probability of CAD based on age, gender, and symptoms is as follows (9):

Low (<10%):

- Asymptomatic men and women of all ages
- Women younger than 50 years with atypical angina

Intermediate (10%–90%):

- Men of all ages with atypical angina
- Women 50 years or older with atypical angina
- Women 30 to 59 years of age with typical angina

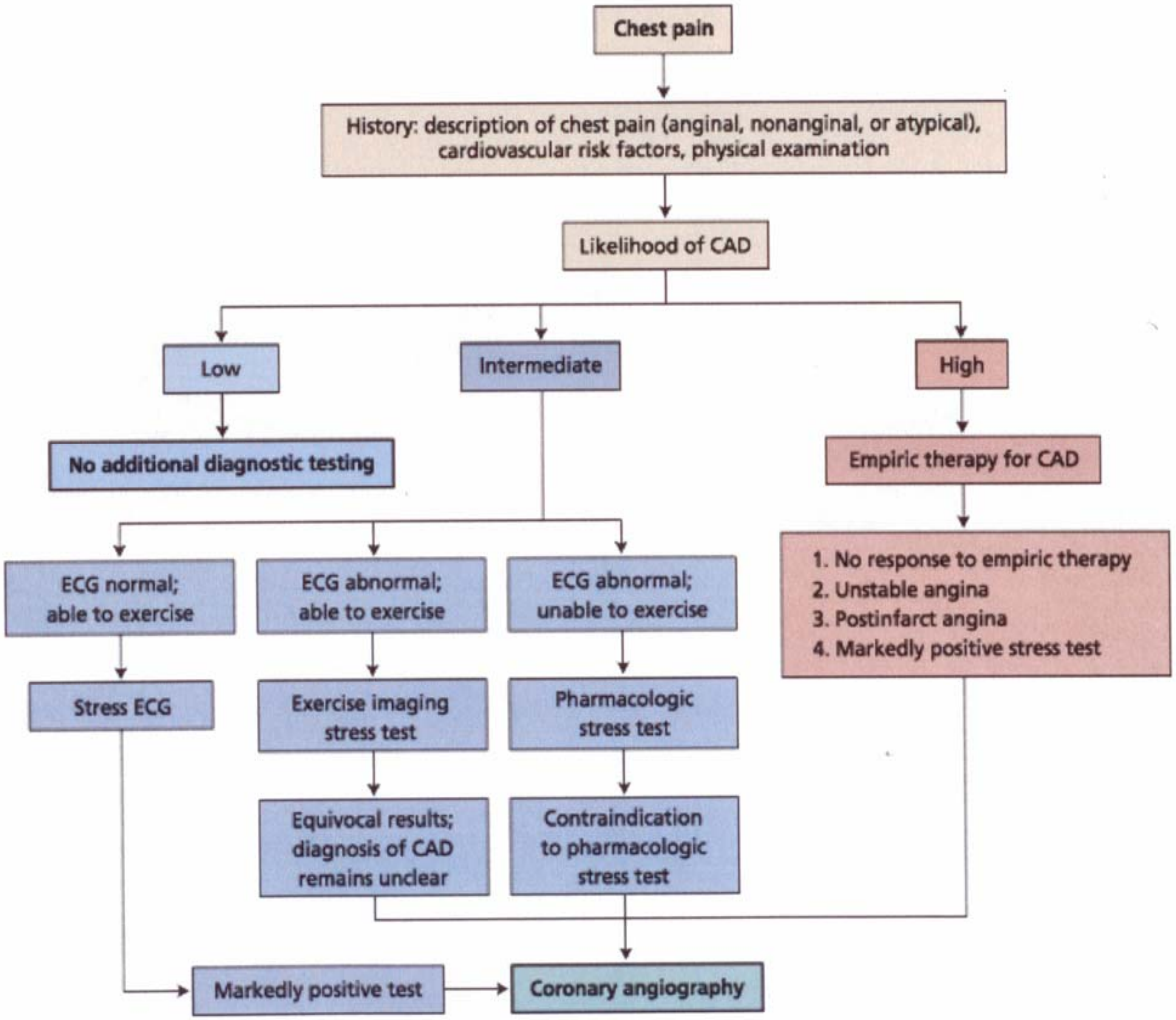
High (>90%):

- Men 40 years or older with typical angina
- Women 60 years or older with typical angina

Noninvasive stress tests for detecting CAD perform best in patients with an intermediate pretest probability of disease. In patients with a high pretest probability of disease, a negative test result is most likely to be falsely negative. In that setting, coronary angiography may be required. In patients with a low pretest probability, a positive stress test result is likely to be falsely positive.

Print Close

Figure 2. Evaluation of Chest Pain



Reprinted with permission from Otto CM, Shavelle DM. Approach to the Cardiovascular Patient. ACP Medicine:2004–2005. Dale DC, Federman DD, eds. New York: WebMD Inc; 2004:191.

ORIGINAL ARTICLE

Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Robert Detrano, M.D., Ph.D., Alan D. Guerci, M.D., J. Jeffrey Carr, M.D., M.S.C.E., Diane E. Bild, M.D., M.P.H., Gregory Burke, M.D., Ph.D., Aaron R. Folsom, M.D., Kiang Liu, Ph.D., Steven Shea, M.D., Moyses Szklo, M.D., Dr.P.H., David A. Bluemke, M.D., Ph.D., Daniel H. O'Leary, M.D., Russell Tracy, Ph.D., Karol Watson, M.D., Ph.D., Nathan D. Wong, Ph.D., and Richard A. Kronmal, Ph.D.

ABSTRACT

BACKGROUND

In white populations, computed tomographic measurements of coronary-artery calcium predict coronary heart disease independently of traditional coronary risk factors. However, it is not known whether coronary-artery calcium predicts coronary heart disease in other racial or ethnic groups.

METHODS

We collected data on risk factors and performed scanning for coronary calcium in a population-based sample of 6722 men and women, of whom 38.6% were white, 27.6% were black, 21.9% were Hispanic, and 11.9% were Chinese. The study subjects had no clinical cardiovascular disease at entry and were followed for a median of 3.8 years.

RESULTS

There were 162 coronary events, of which 89 were major events (myocardial infarction or death from coronary heart disease). In comparison with participants with no coronary calcium, the adjusted risk of a coronary event was increased by a factor of 7.73 among participants with coronary calcium scores between 101 and 300 and by a factor of 9.67 among participants with scores above 300 ($P<0.001$ for both comparisons). Among the four racial and ethnic groups, a doubling of the calcium score increased the risk of a major coronary event by 15 to 35% and the risk of any coronary event by 18 to 39%. The areas under the receiver-operating-characteristic curves for the prediction of both major coronary events and any coronary event were higher when the calcium score was added to the standard risk factors.

CONCLUSIONS

The coronary calcium score is a strong predictor of incident coronary heart disease and provides predictive information beyond that provided by standard risk factors in four major racial and ethnic groups in the United States. No major differences among racial and ethnic groups in the predictive value of calcium scores were detected.

From the University of California at Irvine, Irvine (R.D., N.D.W.); Saint Francis Hospital, Roslyn, NY (A.D.G.); Wake Forest Baptist Medical Center, Winston-Salem, NC (J.J.C., G.B.); the Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD (D.E.B.); the University of Minnesota, Minneapolis (A.R.F.); Northwestern University, Chicago (K.L.); Columbia University, New York (S.S.); Johns Hopkins University, Baltimore (M.S., D.A.B.); Caritas Carney Hospital, Dorchester, MA (D.H.O.); the University of Vermont, Burlington (R.T.); the University of California at Los Angeles, Los Angeles (K.W.); and the University of Washington, Seattle (R.A.K.). Address reprint requests to Dr. Detrano at the Department of Radiological Sciences, University of California at Irvine, Medical Sciences Bldg., Irvine, CA 92697, or at robert@chinacal.org.

N Engl J Med 2008;358:1336-45.

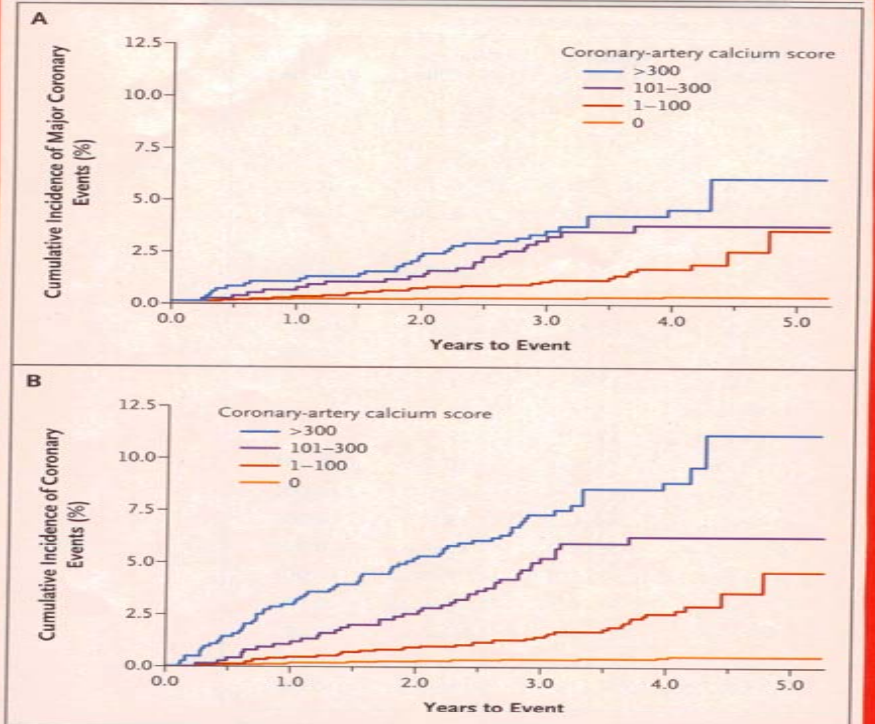


Figure 1. Unadjusted Kaplan–Meier Cumulative-Event Curves for Coronary Events among Participants with Coronary-Artery Calcium Scores of 0, 1 to 100, 101 to 300, and More Than 300.

Panel A shows the rates for major coronary events (myocardial infarction and death from coronary heart disease), and Panel B shows the rates for any coronary event. The differences among all curves are statistically significant ($P<0.001$).

Table 3. Risk of Coronary Events Associated with Increasing Coronary-Artery Calcium Score after Adjustment for Standard Risk Factors.*

Coronary-Artery Calcium Score	Major Coronary Event†			Any Coronary Event		
	No./No. at Risk	Hazard Ratio (95% CI)	P Value	No./No. at Risk	Hazard Ratio (95% CI)	P Value
0	8/3409	1.00		15/3409	1.00	
1–100	25/1728	3.89 (1.72–8.79)	<0.001	39/1728	3.61 (1.96–6.65)	<0.001
101–300	24/752	7.08 (3.05–16.47)	<0.001	41/752	7.73 (4.13–14.47)	<0.001
>300	32/833	6.84 (2.93–15.99)	<0.001	67/833	9.67 (5.20–17.98)	<0.001
$Log_2(CAC+1)$‡		1.20 (1.12–1.29)	<0.001		1.26 (1.19–1.33)	<0.001

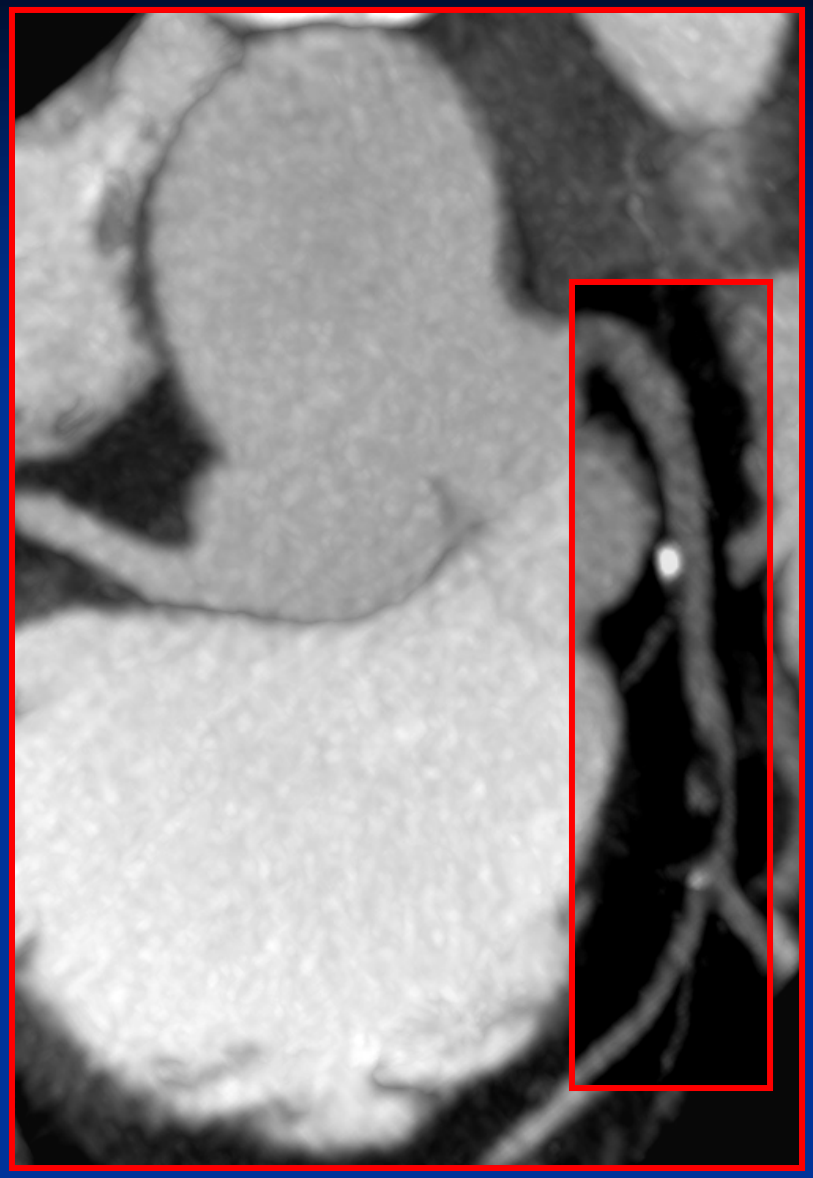
* CAC denotes coronary-artery calcium score, and CI confidence interval.
† Major coronary events were myocardial infarction and death from coronary heart disease.
‡ Each unit increase in $log_2(CAC+1)$ represents a doubling of the coronary-artery calcium score.

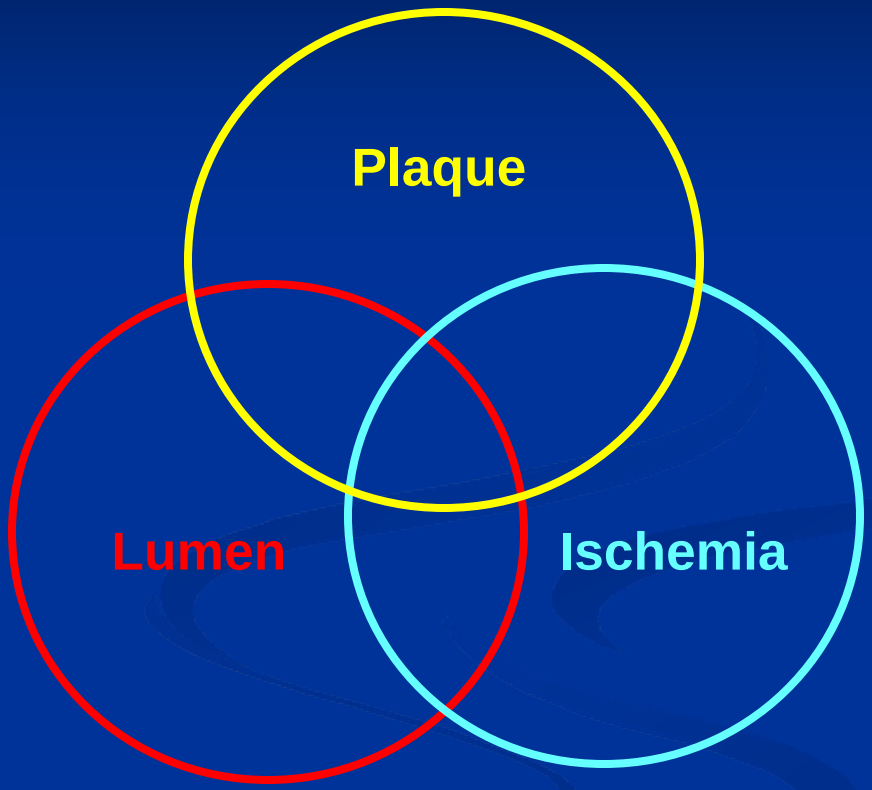
Our current tests for dx CAD

- Stress test 60% accurate
- Cardiac SPECT Imaging
  - 40% have Attenuation Defects
  - Sensitivity 87%
  - Specificity 75%
- Nuclear stress test (functional test) 80-85% accurate, diagnosis Ischemia---good prognostic predictor

Our current tests for dx CAD
Cardiac Cath

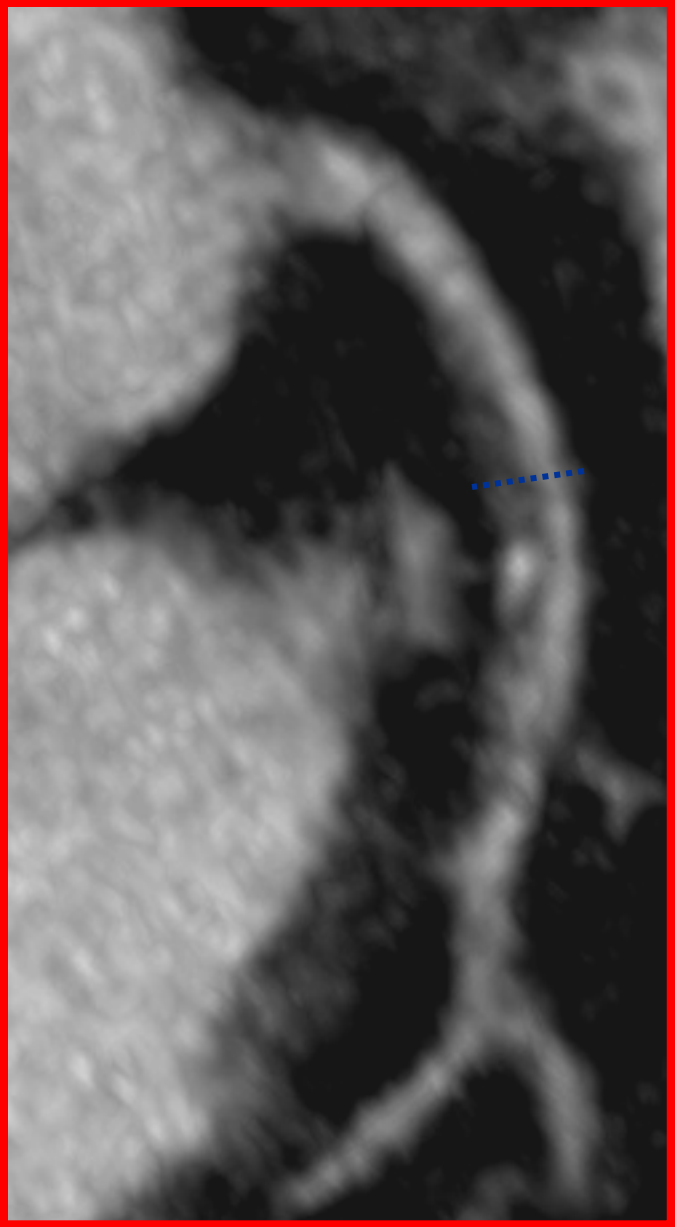
- Cardiac Cath (lumanogram) can miss CAD, good for % stenosis
- ~25% are Normal
- ~8 Million Caths/yr at $4000/Cath
- ~$4 Billion/yr

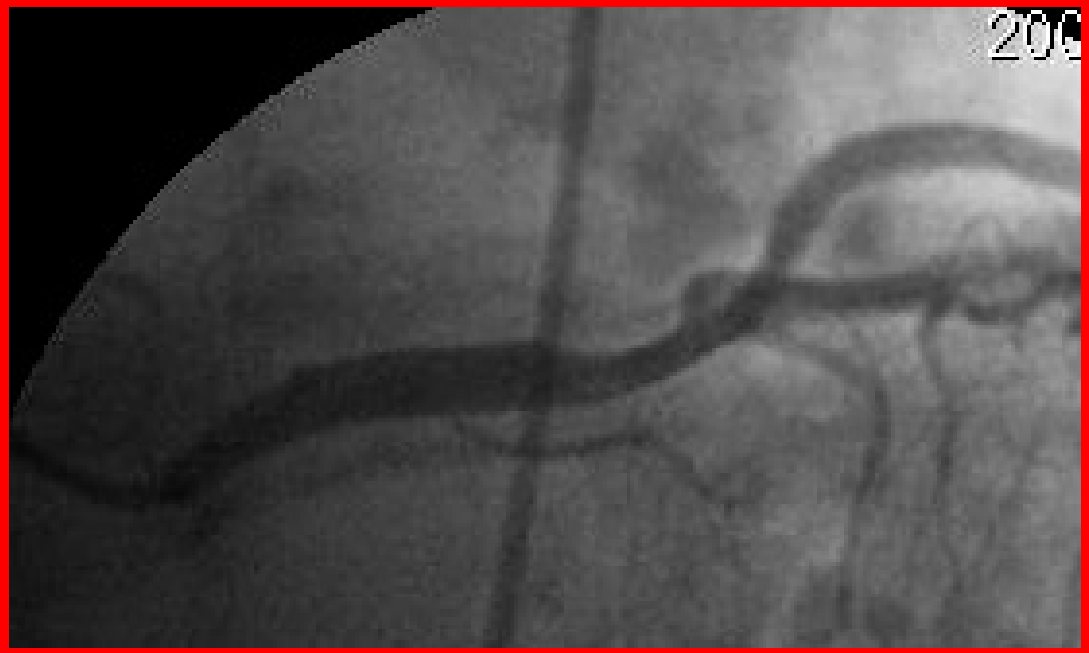



Plaque
Lumen
Ischemia

39 y.o. female with 3 months of heartburn and exertional chest pressure.

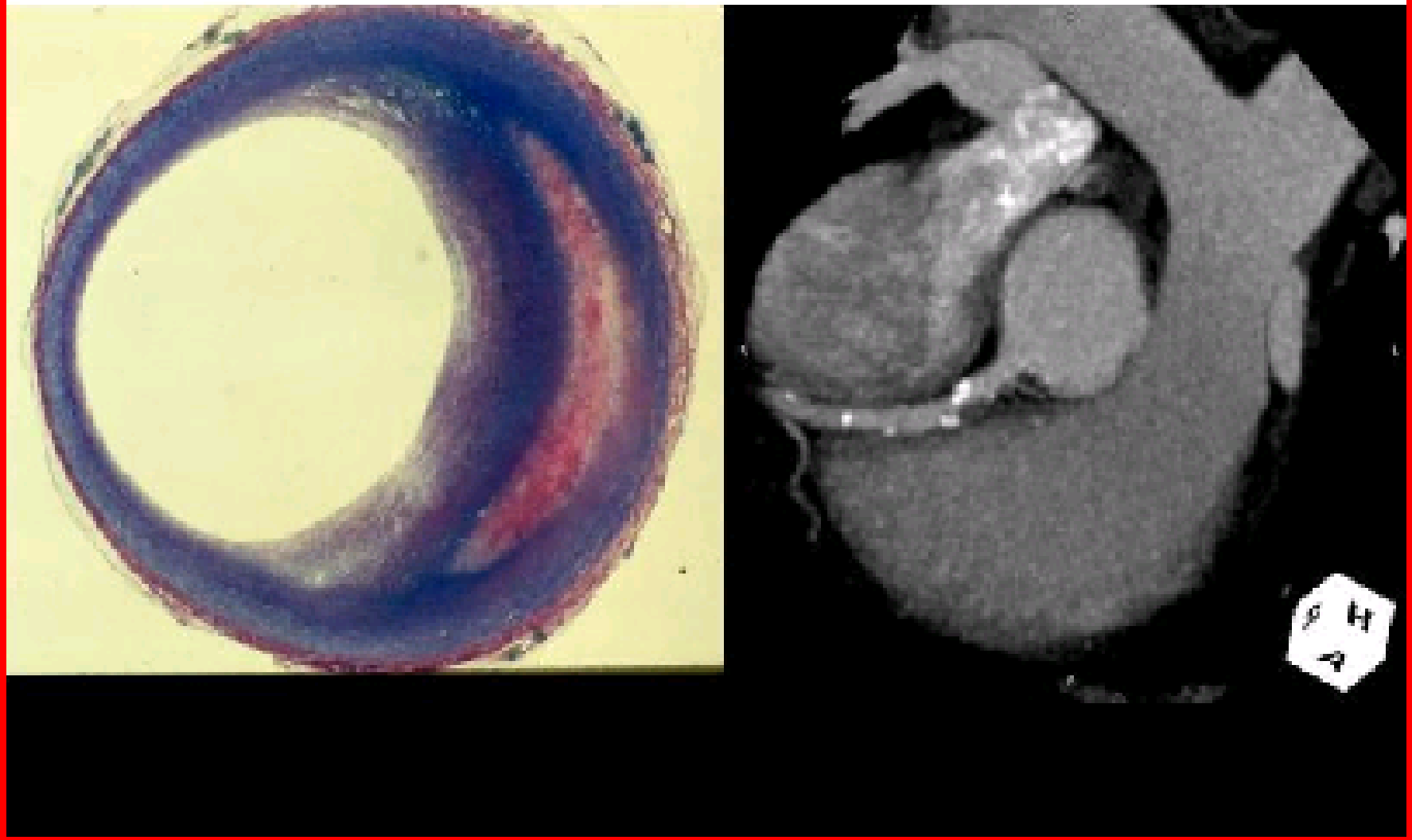
Risks: HTN, Chol and Smoker.



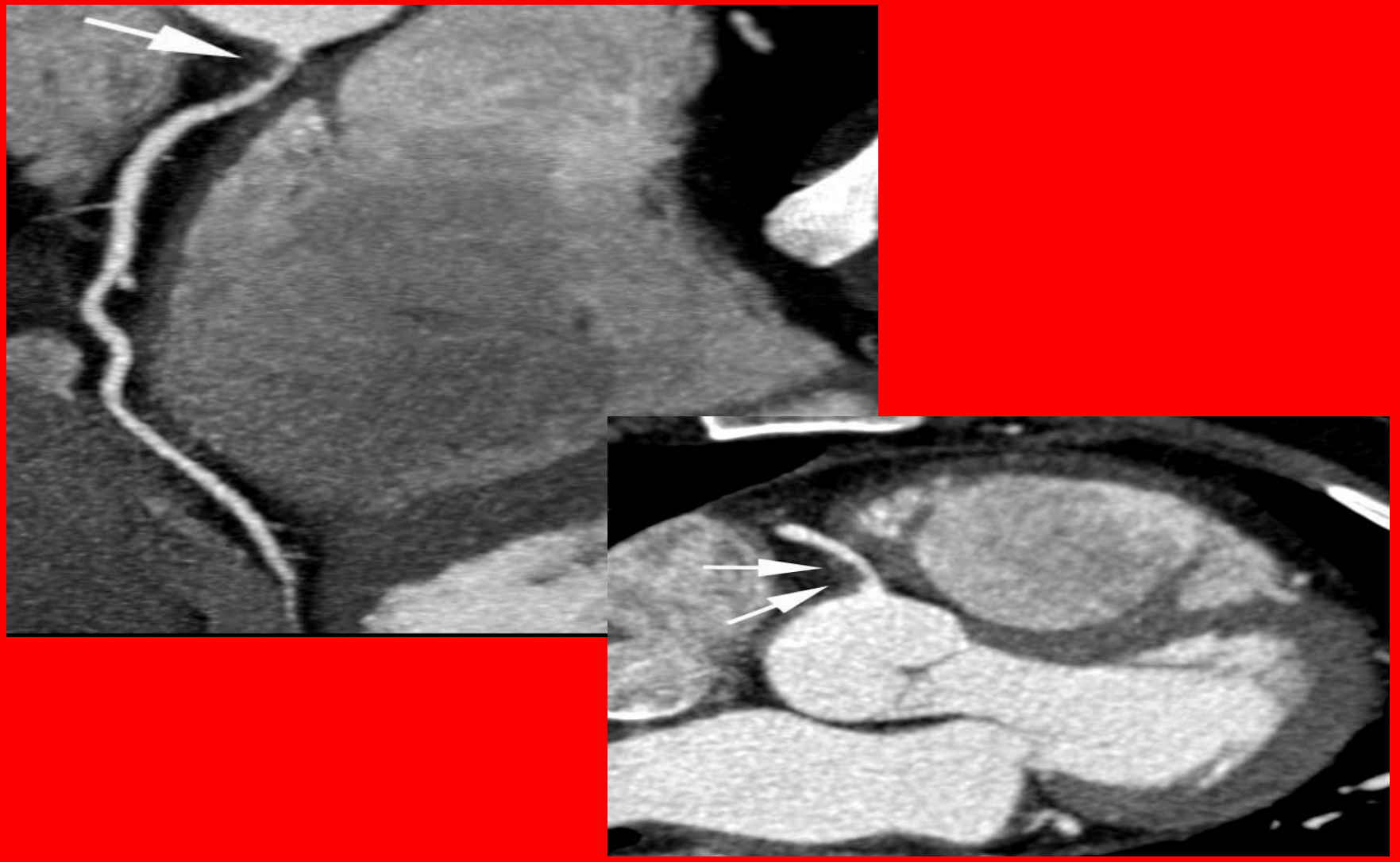


Potential Benefits

Early Detection of Cardiovascular Disease

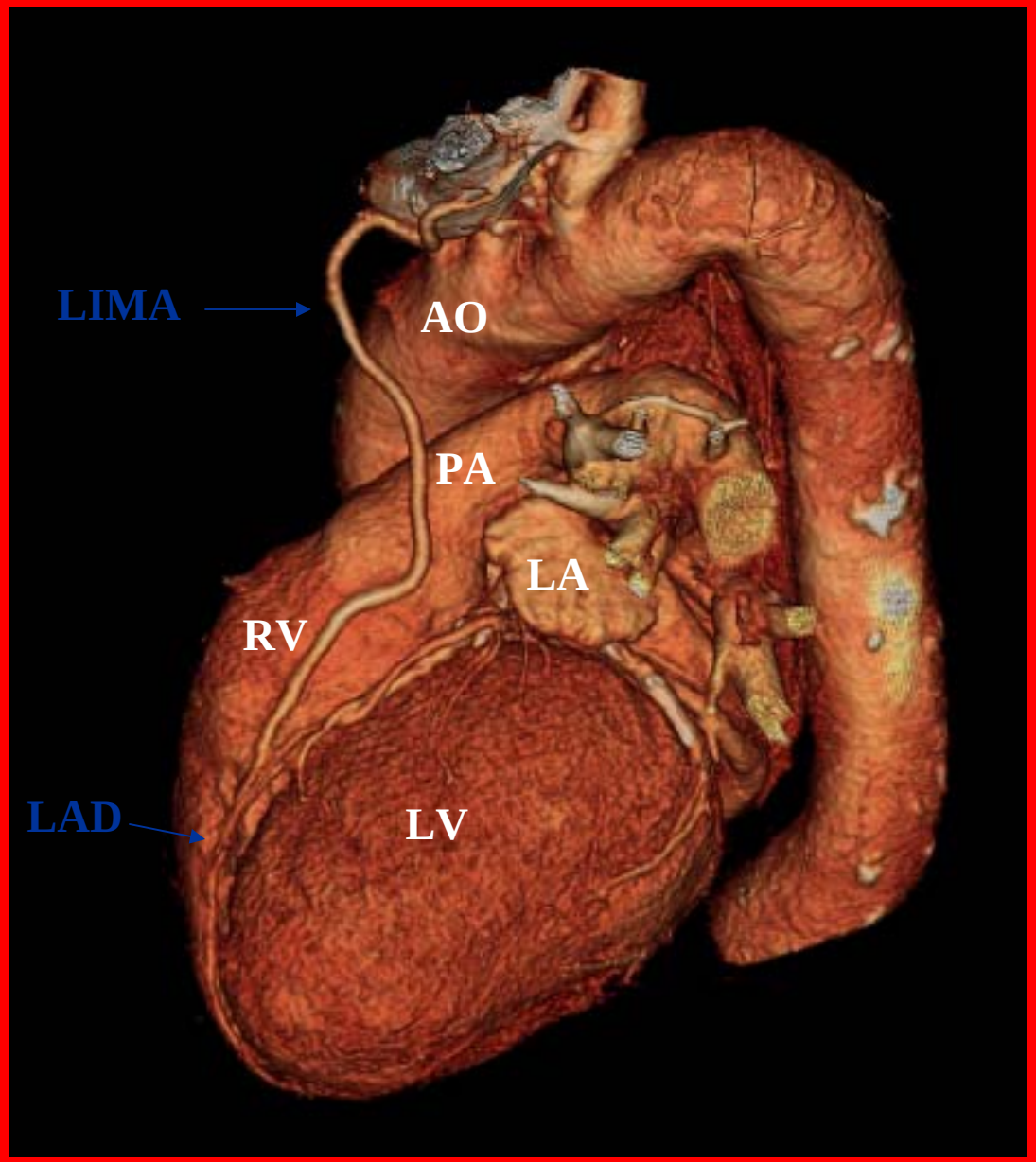


Soft Plaque – RCA Origin



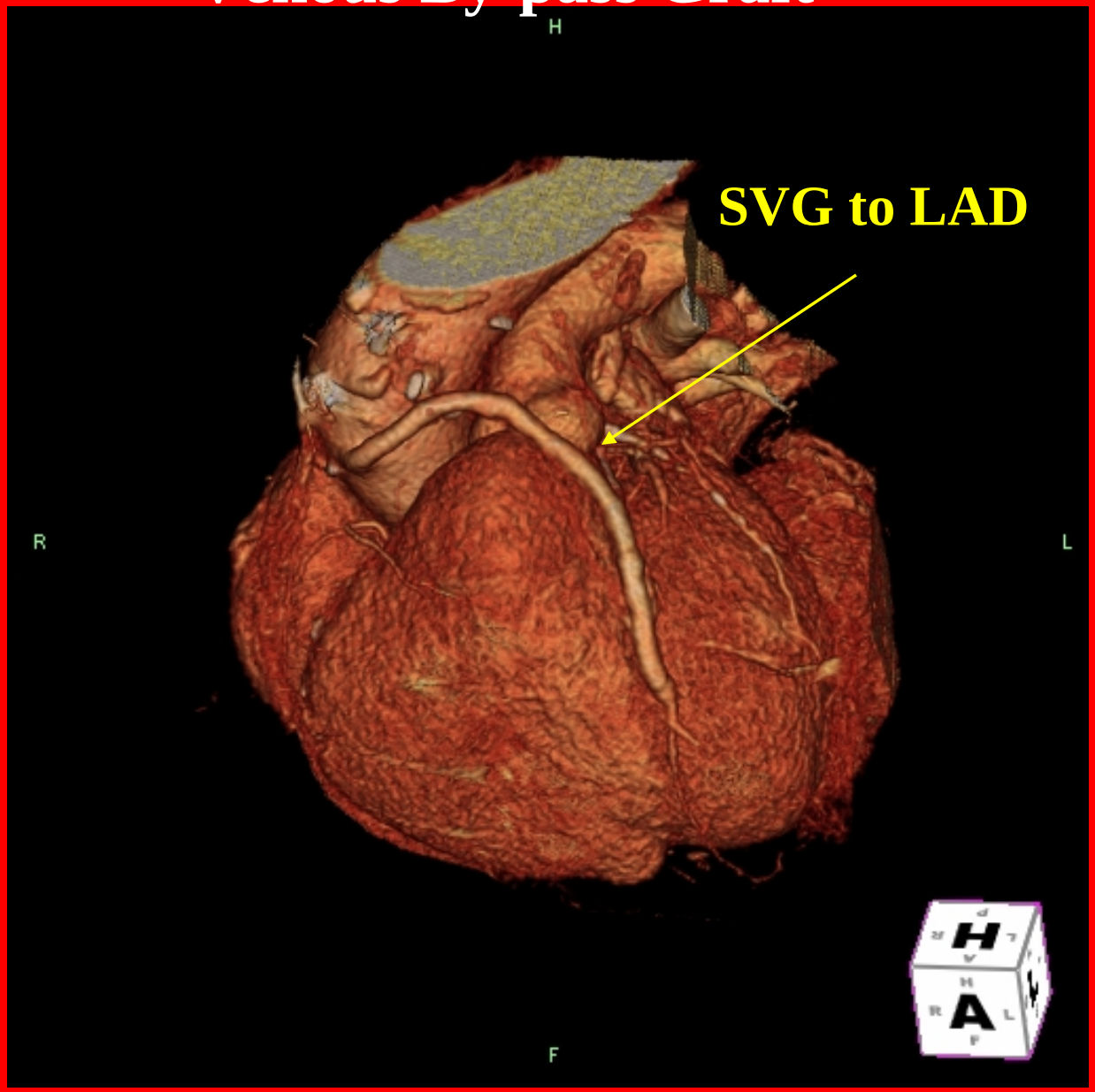
Courtesy of University of Erlangen, Germany

1A



GRAFT PATENCY EVALUATION

Venous By-pass Graft



Cardiovascular Medicine: Item 95

Related Syllabus | Normal Lab Reference

A 55-year-old man is evaluated for epigastric discomfort that has been increasing in frequency despite the use of antacids. The discomfort occurs with exercise, but at times he is able to exercise without provocation of his symptoms. He has no other medical conditions and takes only an 81-mg aspirin daily and occasional chondroitin sulfate for joint aches.

Physical examination, including vital signs and cardiac examination, is normal. Electrocardiogram shows normal sinus rhythm with normal waveforms. Lipid tests show total cholesterol of 199 mg/dL (5.15 mmol/L), LDL cholesterol of 131 mg/dL (3.39 mmol/L), and HDL cholesterol of 35 mg/dL (0.91 mmol/L).

What is the most appropriate next step in the evaluation of this patient?

A ◯ Measurement of C-reactive protein
B ◯ Measurement of coronary calcium by electron-beam CT
C ◯ Measurement of serum homocysteine
D ◯ Exercise electrocardiographic stress test
E ◯ Exercise echocardiogram

Next Item >

Cardiovascular Medicine: Item 95

Related Syllabus | Normal Lab Reference

A 55-year-old man is evaluated for epigastric discomfort that has been increasing in frequency despite the use of antacids. The discomfort occurs with exercise, but at times he is able to exercise without provocation of his symptoms. He has no other medical conditions and takes only an 81-mg aspirin daily and occasional chondroitin sulfate for joint aches.

Physical examination, including vital signs and cardiac examination, is normal. Electrocardiogram shows normal sinus rhythm with normal waveforms. Lipid tests show total cholesterol of 199 mg/dL (5.15 mmol/L), LDL cholesterol of 131 mg/dL (3.39 mmol/L), and HDL cholesterol of 35 mg/dL (0.91 mmol/L).

What is the most appropriate next step in the evaluation of this patient?

A ○ Measurement of C-reactive protein
B ○ Measurement of coronary calcium by electron-beam CT
C ○ Measurement of serum homocysteine
D ◉ **Exercise electrocardiographic stress test**
E ○ Exercise echocardiogram

Answer and Critique (Correct Answer = D)

Based on his sex and the presence of atypical angina, this patient has an intermediate pretest probability of coronary artery disease. The pretest probability is low in asymptomatic men and women of all ages and in women younger than 50 years with atypical angina. Pretest probability increases to an intermediate level (10% to 90%) in men of all ages with atypical angina, women 50 years or older with atypical angina, and women 30 to 59 years of age with typical angina. Pretest probability further increases in men 40 years or older and in women 60 years or older who report typical anginal symptoms. Noninvasive stress testing with or without an imaging modality is the most efficacious method for detecting coronary artery disease in patients with an intermediate pretest probability of disease short of performing

Key Points

- Exercise (or pharmacologic) stress testing is the most sensitive noninvasive method to establish the diagnosis of coronary artery disease.
- Exercise (or pharmacologic) stress cardiac imaging can be used to evaluate for coronary artery disease if the resting electrocardiogram is abnormal.
- The role of electron-beam CT coronary calcium scores is not yet established in the assessment of coronary artery disease.

coronary angiography. In patients with a high pretest probability, a negative test result is most likely to be a false negative. In these patients coronary angiography may be the better test. In patients with low pretest probability, a positive stress test result is likely to be a false positive, and the decision to perform coronary angiography will need to consider all clinical indicators and symptoms.

Exercise stress testing is preferred to pharmacologic stress because the additional information regarding the patient's ability to exercise as well as the hemodynamic responses to exercise can be examined. A failure to increase blood pressure or fall in blood pressure during exercise is associated with severe three-vessel disease or left main disease in some patients and is a marker of high ischemic risk. Exercise methods include upright treadmill, sitting bicycle, and supine bicycle testing.

Pharmacologic stress testing uses agents, such as dobutamine, that mimic the catecholamine increases of exercise, or agents, such as adenosine or dipyridamole, that increase coronary blood flow through coronary artery vasodilation.

Ischemia can be detected using electrocardiographic monitoring when the normal ST segment at rest is depressed or elevated during peak physical activity. A normal baseline electrocardiogram is required for accurate interpretation. In patients with an abnormal baseline electrocardiogram, either echocardiographic or radionuclide imaging during stress is needed for detection of ischemia. Some evidence indicates that a stress imaging study is more accurate than stress electrocardiogram in women; however, the evidence is not sufficiently strong to opt for an imaging test as the first choice in all women.

Elevated serum markers of inflammatory responses suggest an increased risk for coronary artery disease but are not diagnostic for the condition and are not routinely recommended. Patients with high serum levels of homocysteine have greater risk of cardiovascular disease, a finding greatest in persons with impaired renal function.

A coronary artery calcium score measured by electron-beam CT is an independent predictor of adverse cardiovascular events. However the coronary calcium score does not correlate well with angiography or ischemic stress testing because the atherosclerotic coronary artery undergoes initial remodeling, increasing the caliber of the lumen. Calcium scores do not provide data on plaque stability or the potential for plaque activation and myocardial infarction. The precise role of electron-beam CT calcium scores is still being defined. Electron-beam CT may be useful, especially if negative, to reassure the low-risk patient. In patients with a high pretest probability of coronary artery disease, the calcium score does not affect their management.

Bibliography

1. **Mattera JA, Arain SA, Sinusas AJ, Finta L, Wackers FJ.** Exercise testing with myocardial perfusion imaging in patients with normal baseline electrocardiograms: cost savings with a stepwise diagnostic strategy. J Nucl Cardiol. 1998;5:498-506. [PMID: 9796897] [PubMed]

Cardiovascular Medicine: Item 88

Related Syllabus | Normal Lab Reference

A 64-year-old man is evaluated in the emergency department for epigastric chest discomfort and episodes of dyspnea with moderate activity. The discomfort started 2 days ago and has been intermittent, occurring mostly at rest. He works in an office and is relatively inactive. He had been using antacids for several months with variable response. He has no significant medical history and takes no other medications.

Blood pressure is 150/85 mm Hg and heart rate is 81/min; there is no jugular vein distention or carotid bruits; cardiac examination reveals a normal S_1 and S_2, with no murmur, gallop, or clicks. Examination of the abdomen and extremities is normal. Electrocardiogram shows flattened T waves. He is treated with enoxaparin, a β-blocker, aspirin, and sublingual nitroglycerin and admitted to the chest pain unit for observation. Serial measurements of cardiac enzymes are normal, and there are no changes on the subsequent two electrocardiograms.

Echocardiogram shows a left ventricular ejection fraction of 35% to 40% with global hypokinesis and mild mitral regurgitation.

What is the next most appropriate step in the management of this patient?

A ○ Heparin
B ○ Eptifibatide
C ○ Exercise perfusion imaging stress test
D ○ Coronary angiography
E ○ Exercise electrocardiography stress test

Next Item >

Cardiovascular Medicine: Item 88

Related Syllabus | Normal Lab Reference

A 64-year-old man is evaluated in the emergency department for epigastric chest discomfort and episodes of dyspnea with moderate activity. The discomfort started 2 days ago and has been intermittent, occurring mostly at rest. He works in an office and is relatively inactive. He had been using antacids for several months with variable response. He has no significant medical history and takes no other medications.

Blood pressure is 150/85 mm Hg and heart rate is 81/min; there is no jugular vein distention or carotid bruits; cardiac examination reveals a normal S_1 and S_2, with no murmur, gallop, or clicks. Examination of the abdomen and extremities is normal. Electrocardiogram shows flattened T waves. He is treated with enoxaparin, a β-blocker, aspirin, and sublingual nitroglycerin and admitted to the chest pain unit for observation. Serial measurements of cardiac enzymes are normal, and there are no changes on the subsequent two electrocardiograms.

Echocardiogram shows a left ventricular ejection fraction of 35% to 40% with global hypokinesis and mild mitral regurgitation.

What is the next most appropriate step in the management of this patient?

A ○ Heparin
B ○ Eptifibatide
C ◉ **Exercise perfusion imaging stress test**
D ○ Coronary angiography
E ○ Exercise electrocardiography stress test

Answer and Critique (Correct Answer = C)

This patient has atypical chest pain, which may be gastritis, and a nonspecific history of dyspnea on exertion, which may be related to his decreased left ventricular ejection fraction. Atypical angina without risk factors for coronary artery disease and a normal physical examination constitutes a low risk for coronary artery disease. The depressed left ventricular ejection fraction increases risk. An abnormal electrocardiogram lowers the ability of exercise stress test alone to render an accurate diagnosis. The next step is to evaluate with an exercise perfusion imaging study and if abnormal, proceed to coronary angiography.

Key Points

- In patients with chest pain and intermediate risk of coronary artery disease, non-invasive testing is indicated.
- Patients with chest pain and low coronary artery disease risk with a normal electrocardiogram and a normal exercise electrocardiogram can be discharged without coronary angiography.

The decision to use heparin or eptifibatide is based on the history consistent with unstable angina or chest pain and intermediate- to high-risk features, such as continued angina, decreased left ventricular function, age >65 years, and diabetes mellitus. Immediate coronary angiography would be appropriate if there were high-risk markers such as markedly elevated cardiac enzymes, hypotension, decreased left ventricular function, or new electrocardiographic changes in a patient with unstable angina/non-ST-elevation myocardial infarction.

Bibliography

1. **Boyne TS, Koplan BA, Parsons WJ, Smith WH, Watson DD, Beller GA.** Predicting adverse outcome with exercise SPECT technetium-99m sestamibi imaging in patients with suspected or known coronary artery disease. Am J Cardiol. 1997;79:270-4. [PMID: 9036743] [PubMed]

Next Item >

Cardiovascular Medicine: Item 87

Related Syllabus | Normal Lab Reference

A 35-year-old man with a 20-year history of type 1 diabetes mellitus is undergoing preoperative evaluation for renal transplantation. His clinical course has been complicated by hypertension, diabetic retinopathy, and peripheral neuropathy that limits his ability to walk. His blood pressure is 142/85 mm Hg. His LDL cholesterol is 140 mg/dL (3.62 mmol/L) and his HDL cholesterol is 30 mg/dL (0.78 mmol/L). He currently smokes a half of a pack of cigarettes daily. His electrocardiogram is shown (Figure 87). Medical consultation is requested for evaluation of his preoperative cardiovascular risk.

Which of the following is the most appropriate recommendation at this time?

A ○ No further evaluation is needed
B ○ Serum C-reactive protein level
C ○ 24-hour electrocardiographic monitoring
D ○ Pharmacologic stress nuclear study
E ○ Coronary angiography

Next Item >

Cardiovascular Medicine: Item 87

Related Syllabus | Normal Lab Reference

A 35-year-old man with a 20-year history of type 1 diabetes mellitus is undergoing preoperative evaluation for renal transplantation. His clinical course has been complicated by hypertension, diabetic retinopathy, and peripheral neuropathy that limits his ability to walk. His blood pressure is 142/85 mm Hg. His LDL cholesterol is 140 mg/dL (3.62 mmol/L) and his HDL cholesterol is 30 mg/dL (0.78 mmol/L). He currently smokes a half of a pack of cigarettes daily. His electrocardiogram is shown (Figure 87). Medical consultation is requested for evaluation of his preoperative cardiovascular risk.

Which of the following is the most appropriate recommendation at this time?

- A ○ No further evaluation is needed
- B ○ Serum C-reactive protein level
- C ○ 24-hour electrocardiographic monitoring
- **D ◉ Pharmacologic stress nuclear study**
- E ○ Coronary angiography

Answer and Critique (Correct Answer = D)

Key Points

- The risk of coronary artery disease in diabetic patients is 2 to 4 times higher than in nondiabetic patients.
- The pretest likelihood of disease should be calculated using available algorithms in patients with coronary risk factors.

In this patient with diabetes, dyslipidemia, smoking, and hypertension, the Framingham 10-year likelihood of a cardiac event is 18%, compared to an average event rate of 5% for men of this age. In addition, diabetic patients frequently do not have angina despite the presence of ischemia (silent ischemia). This patient's electrocardiogram is consistent with left ventricular hypertrophy, based on an S wave in lead V_2 plus an R wave in lead V_6 > 35 mV, left axis deviation, and lateral ST-T changes. Left atrial enlargement also is present. Because the transplant team would defer transplantation until after coronary revascularization if significant disease were present, further evaluation is needed. A pharmacologic stress nuclear study is an appropriate diagnostic approach that provides information on the presence and severity of coronary ischemia. Exercise electrocardiographic stress testing would be less useful in this patient because his ability to exercise could be limited by peripheral neuropathy; in addition, the baseline electrocardiogram would likely show resting ST-segment changes due to left ventricular hypertrophy. Serum C-reactive protein levels are a marker of systemic inflammation, and population-based studies have demonstrated that elevated levels

are associated with an increased risk of coronary disease. However, C-reactive protein levels are not helpful in detection of inducible ischemia in an individual patient. Although a 24-hour electrocardiogram could show ST-segment changes in a patient with silent ischemia, this approach is less sensitive and specific than stress testing, and its value would be limited in this patient with an abnormal resting electrocardiogram. Coronary angiography provides definitive evaluation of coronary anatomy and would likely demonstrate coronary artery disease in this patient. However, most clinicians would perform a stress imaging study first, both for diagnosis and to target which vessel should be considered for revascularization if multiple lesions are present.

Bibliography

1. **Almdal T, Scharling H, Jensen JS, Vestergaard H.** The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med. 2004;164:1422-6. [PMID: 15249351] [PubMed]
2. **Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al.** Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004;141:421-31. [PMID: 15381515] [PubMed]
3. Estimating coronary heart disease (CHD) risk using Framingham Heart Study prediction score sheets. National Heart, Blood, and Lung Institute, National Institutes of Health, Bethesda, MD. Available at: http://www.nhlbi.nih.gov/about/framingham/riskabs.htm. Accessed 19 Sep 2006.

Next Item >

Cardiovascular Medicine: Item 102

Related Syllabus | Normal Lab Reference

A 45-year-old man is evaluated in the emergency department for chest pain. He never had chest pain before, but over the past few days he has experienced several episodes of chest tightness with exercise. He has a history of hypertension and tobacco use. He takes 1 aspirin daily.

On examination, the patient's blood pressure is 140/80 mm Hg and the cardiovascular examination is normal. The initial electrocardiograph is normal. Troponin is elevated. The patient is treated with aspirin and intravenous β-blockers.

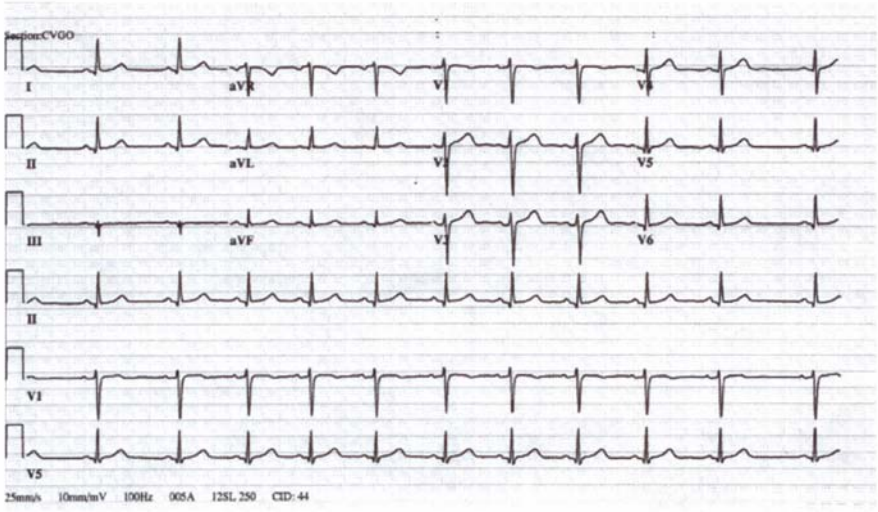
During his examination in the emergency department, the patient develops another episode of chest discomfort, with radiation to the left upper extremity and dyspnea. The physical examination while the pain is occurring demonstrates an S_4. After giving the patient a sublingual nitroglycerin tablet, which relieves the pain, an electrocardiogram is obtained and is shown (Figure 102). Intravenous heparin is added to the treatment.

What diagnostic test should be done next?

A ○ Exercise electrocardiogram
B ○ Exercise echocardiogram
C ○ Electron beam CT
D ○ Adenosine nuclear study
E ○ Coronary angiography

Next Item >

Print Close



Cardiovascular Medicine: Item 102

Related Syllabus | Normal Lab Reference

A 45-year-old man is evaluated in the emergency department for chest pain. He never had chest pain before, but over the past few days he has experienced several episodes of chest tightness with exercise. He has a history of hypertension and tobacco use. He takes 1 aspirin daily.

On examination, the patient's blood pressure is 140/80 mm Hg and the cardiovascular examination is normal. The initial electrocardiograph is normal. Troponin is elevated. The patient is treated with aspirin and intravenous β-blockers.

During his examination in the emergency department, the patient develops another episode of chest discomfort, with radiation to the left upper extremity and dyspnea. The physical examination while the pain is occurring demonstrates an S_4. After giving the patient a sublingual nitroglycerin tablet, which relieves the pain, an electrocardiogram is obtained and is shown (Figure 102). Intravenous heparin is added to the treatment.

What diagnostic test should be done next?

- A ○ Exercise electrocardiogram
- B ○ Exercise echocardiogram
- C ○ Electron beam CT
- D ○ Adenosine nuclear study
- **E ◉ Coronary angiography**

Answer and Critique (Correct Answer = E)

Key Points

- Coronary angiography is indicated in patients with a history of unstable angina or non-ST-elevation myocardial infarction.
- In patients with a high pretest probability of coronary artery disease, a negative stress test result is most likely to be false.

This patient has a history of progressive, unstable angina and elevated troponin, suggesting a non-ST-elevation myocardial infarction. The initial electrocardiogram, obtained when the patient was pain-free, was normal. High-risk patients with unstable angina or non-ST-elevation myocardial infarction benefit from a strategy of early invasive coronary angiography, as compared with a more conservative approach involving risk stratification using predischarge exercise testing. Early coronary angiography allows the identification of high-risk coronary artery disease, including left main or three-vessel disease and other high-risk features such as coronary thrombus or plaque ulceration. In addition, left ventricular function is usually measured during

angiography, and early coronary revascularization can be performed if indicated.

The physical examination performed during chest pain demonstrates an S_4 that was not audible in the absence of chest pain. An S_4 is caused by left atrial filling against a left ventricle stiffened by ischemia and thus supports ischemia as a cause of chest pain.

Both pharmacologic and exercise-based stress testing are contraindicated in the setting of unstable angina. In addition, even if unstable angina were not present in this patient, the pretest probability of coronary artery disease is high, and thus a negative stress test result would most likely be false.

The use of electron-beam CT is controversial in patients with chest pain. It is primarily suggested for low-risk patients as screening tool. In this patient, the pretest probability of coronary artery disease is high and the calcium score thus would not affect the management of this patient.

Bibliography

1. **Braunwald E, Antman E, Beasley J.** ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update Guidelines on the Management of Patients with Unstable Angina) (2002) American College of Cardiology Web site. Available at: http://www.acc.org/qualityandscience/clinical/statements.htm. Accessed September 19, 2006
2. **Keelan PC, Bielak LF, Ashai K, Jamjoum LS, Denktas AE, Rumberger JA, et al.** Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation. 2001;104:412-7. [PMID: 11468202] [PubMed]
3. **O'Rourke RA, Brundage BH, Froelicher VF, Greenland P, Grundy SM, Hachamovitch R, et al.** American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. J Am Coll Cardiol. 2000;36:326-40. [PMID: 10898458] [PubMed]

Next Item >